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Synthesis of Complanadine A and Phthaloyl Peroxide-Mediated Oxidations of Alkenes and Arenes

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Synthesis of Complanadine A and Phthaloyl Peroxide-Mediated Oxidations of Alkenes and Arenes

by

Changxia Yuan, B.S.

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Journeying is hard,

Journeying is hard.

There confront many turnings,

Which am I to follow?

Hanging cloud sail,

I mount the wind and cleave the waves,

bridging my sea someday.-Bai Li

长风破浪会有时，

直挂云帆济苍海。

李白

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Synthesis of Complanadine A and Phthaloyl Peroxide-Mediated Oxidations of Alkenes and Arenes

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The University of Texas at Austin, 2013

Supervisor: Dionicio Siegel

The natural product complanadine A has shown promise in regenerative science, promoting neuronal outgrowth by inducing the secretion of growth factors from glial cells. Through the use of tandem, cobalt-mediated [2+2+2] cycloaddition reactions two synthetic routes have been developed with different sequences for the formation of the unsymmetric bipyridyl core. The regioselective formation of each of the pyridines was achieved based on the inherent selectivity of the molecules or by reversing this inate regioselectivity through the addition of Lewis bases. This strategy has been successfully employed to provide laboratory access to complanadine A as well as structurally related compounds possessing the lycodine core.

Phthaloyl peroxide derivatives have the potential to function as organocatalysts for the dihydroxylation of alkenes. The development of an organocatalytic system for the *syn*-dihydroxylation of alkenes, using hydrogen peroxide as the stoichiometric oxidant,

could minimize the waste and cost associated with the current industrial process. With new access to phthaloyl peroxide derivatives, this dihydroxylation method was improved with stoichiometric dichlorophthaloyl peroxide for the dihydroxylation of alkenes.

Substituted phenols are broadly useful compounds, functioning as starting materials and end products in all areas of chemical industry. Since the initial discovery of phenol from coal tar advances have been made in the synthetic preparations of this class of compounds which possess a hydroxyl group appended to an aromatic hydrocarbon core. Ideally the synthesis of phenols is achieved through the direct installation of oxygen into an aromatic precursor, which is typically more abundant. In this thesis it is discussed how phthaloyl peroxide, in the absence of other reagents, enables the conversion of aromatic hydrocarbons to phenols even when the precursors possess functionality that is incompatible with strongly oxidizing conditions. The reaction is shown to proceed through a "reverse rebound" mechanism as opposed to the classical rebound mechanism, providing insight into the unique aryl selectivity of the chemical transformation.

Table of Contents

List of Tables

List of Figures

List of Scheme

Abbreviations

2D-NMR	two dimensional nuclear magnetic resonance
AcOH	acetic acid
atm	atmosphere
$BF_3{\cdot}OEt_2$ boron	trifluoride diethyl etherate
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CI	chemical ionization
CO	carbon monoxide
D	dextrorotatory
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
equiv	equivalent
ESI	electrospray ionization
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate

EtOH	ethanol
g	gram
h	hour
HF	hydrogen fluoride
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant
K_2CO_3	potassium carbonate
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LiHMDS	lithium hexamethyldisilazide
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
MOM	methoxymethyl
MsCl	methanesulfonyl chloride

MS	mass spectrometry
MS-4Å	4 angstrom molecular sieves
NaCl	sodium chloride
$NaHCO_3$	sodium hydrogen carbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NBS	*N*-bromosuccinimide
n-BuLi	normal butyllithium
NH_4Cl	ammonium chloride
nM	nanomolar
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OAc	acetate
OBz	benzoate
p	*para*
PhMe	toluene
pin	pinacolate
PMHS	polymethylhydrosiloxane
PPh_3	triphenylphosphine
ppm	parts per million
R_f	retention factor
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride

TBSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TMSOTf	trimethylsilyl trifluoromethanesulfonate

CHAPTER 1 Background for (–)-Complanadine A and (+)-Lycodine

1.1 Isolation and Structural Characterization of Complanadine A

Lycopodium alkaloids are natural products with unique annulated ring systems and they have attracted scientific inquiry based on their biogenesis, biology, and as targets for chemical synthesis.[1] In 1958 lycodine was isolated by Anet and Eves from *Lycopodium annotinum L.*, *Lycopodiaceae*.[2] Later, in 1960, Ayer and coworkers identified the structure of lycodine **1.1** as possessing a transannular skeleton fused with a pyridyl ring and it was given the IUPAC name [4a*R*-(4aa,5a,10ba,12*R*')]-2,3,4,4a,5,6-hexahydro-12-methyl-1*H*-5,10b-propano-1,7-phenanthroline (Figure 1.1).[3] Subsequently, related *Lycopodium* alkaloids were isolated and their structures elucidated. In 2000 Kobayashi and coworkers examined the club moss *Lycopodiumserratum var. serratum* and isolated a dimeric alkaloid with a pseudo-symmetrical lycodine skeleton that was later named as complanadine A (Figure 1.2).[4]

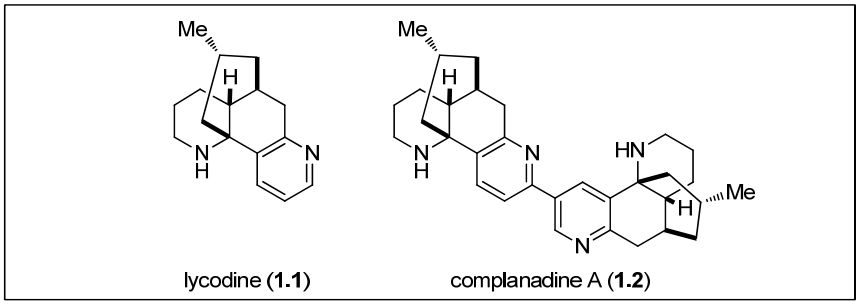


Figure 1.1. Lycodine (**1.1**) and complanadine A (**1.2**).

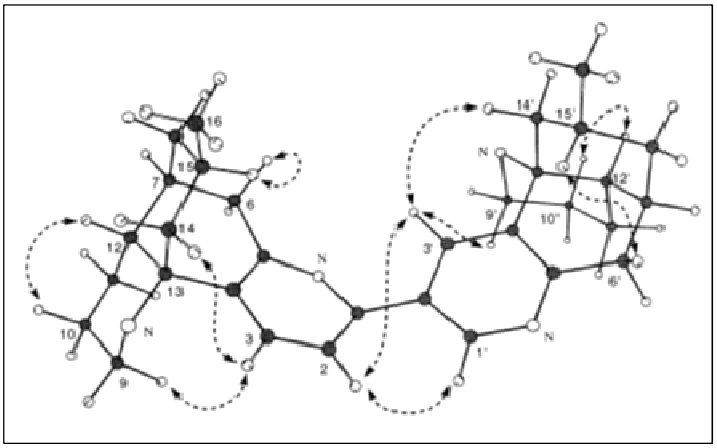


Figure 1.2. NOE analysis of complanadine A (**1.2**).

Kobayashi and coworkers subsequently isolated complanadines B (**1.3**), C (**1.4**), D (**1.5**) and E (**1.6**) (Figure 1.3).[5] Interstingly, the structures of complanadine B to E possessed diffrent oxidation states with complanadine C possessing a rearranged skeleton (complanadine C **1.4**).

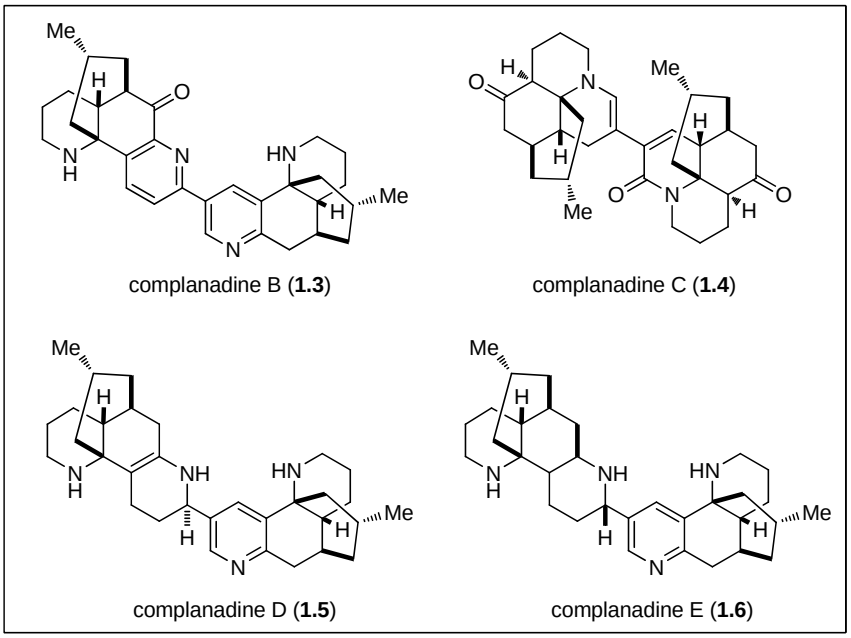


Figure 1.3. Complanadines B through E.

1.2 Biological Activity of Complanadine A

Gene therapy-based approaches to increasing the production of neurotrophic factors, while promising, have not overcome the limitations of short-lived effects, undesirable immune responses, intracranial delivery, and challenges involving the use of viral vectors. Our group has an interest in using small molecules to provide an alternative approach, relative to biologics, to promote regeneration.[6] Able to mimic neurotrophic factors, or to induce neurotrophic factor biosynthesis, small molecules possess a pharmacological advantage. Along these lines it was discovered that the natural product complanadine A (**1.2**) and complanadine B (**1.3**), induced the secretion of neurotrophic factors from 1321N1 cells (human glial cells derived from brain astrocytoma), promoting the differentiation of PC-12 cells.[7] The enhanced expression of NGF mRNA by 1321N1 cells treated with complanadine B was determined by semiquantitative RT-PCR.[8]

1.3 Proposed Biosynthetic Pathway

Defined by A. W. Ayer,[1b] the lycopodium alkaloids can be separated into four classes: lycodine, lycopodine, fawcettimine, and miscelaneous derivatives (Figure 1.4). The biosynthesis of these compounds has been based on Conroy's biogenetic hypothesis.[8] Based on these observation one can us the different oxidation states to differentiate the four major classes of lycopodium natural products.

In Figure 1.5 the biosynthesis is outlined. Starting from L-lysine **1.10**, cadaverine **1.11** is formed following a decaboxylation. An oxidase transforms cadaverine **1.11** to 5-aminopentanal **1.12** in equilibrium with piperideine **1.13**. Malonyl-CoA **1.14** dimerizes to give **1.15** which goes on to react with **1.13** to access **1.16**. At this stage **1.19** will be formed after decarboxylation and dimerization. The alkaloids originate from two pelleterine **1.18** units that form the bonds between C-4 and C-13 to give the lycodane skeleton. Under oxidation, the pyridine-based lycodine **1.1** provide the second class. After further oxidation of the pyridine and detaching C-1 from N_{α} and reattaching $N_{\beta,}$ the pyridone skeleton provides the lycopodine class **1.8**. Migration of C-4 from C-13 to C-12 gives the fawcettimine skeleton **1.9**.

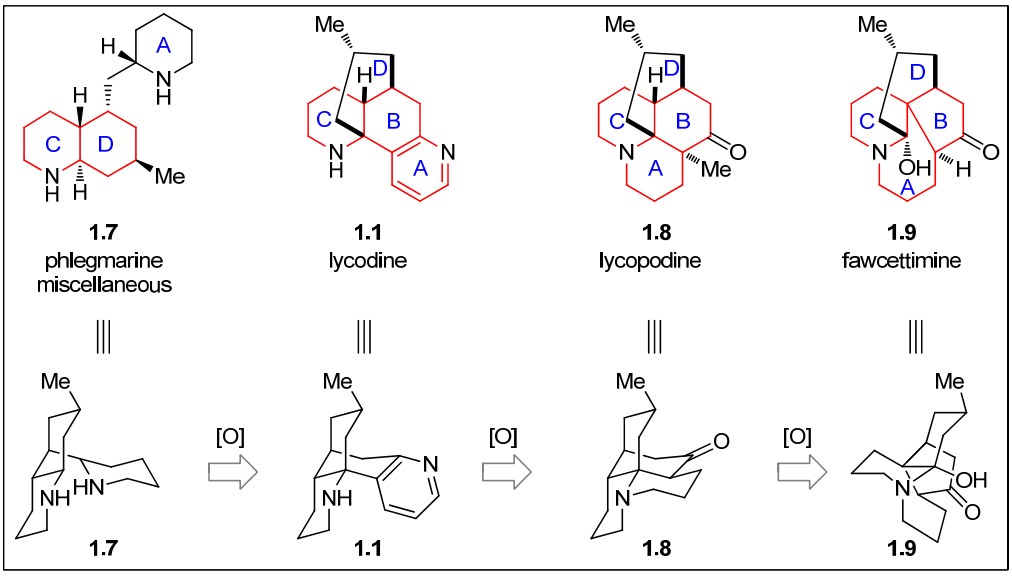


Figure 1.4. Four major lycopodium alkaloids with different oxidation states.

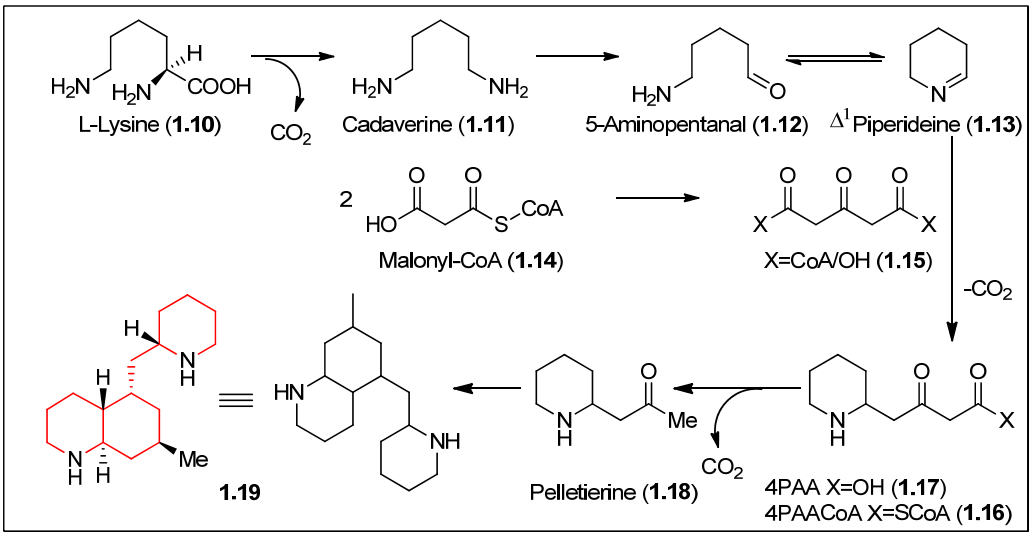


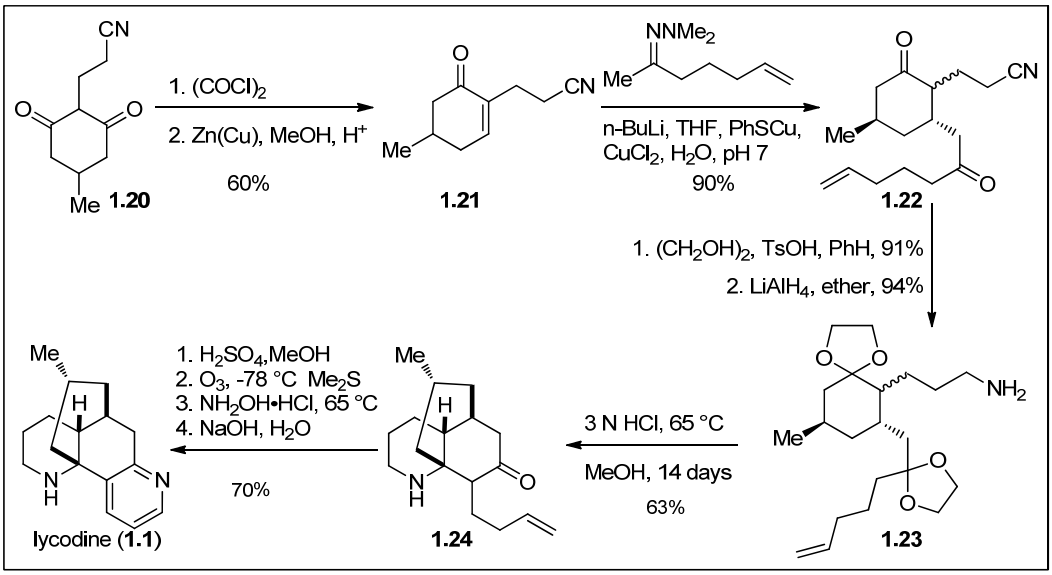
Figure 1.5. Proposed biosynthetic pathway to pelletierine and precursors of the lycopodium alkaloids.

1.4 Previous Syntheses of Lycodine

Lycopodium alkaloids have been extensively studied by synthetic scientists.[9] Relevant to our work these include lycodine, complanadine A[15] and complanadine B.

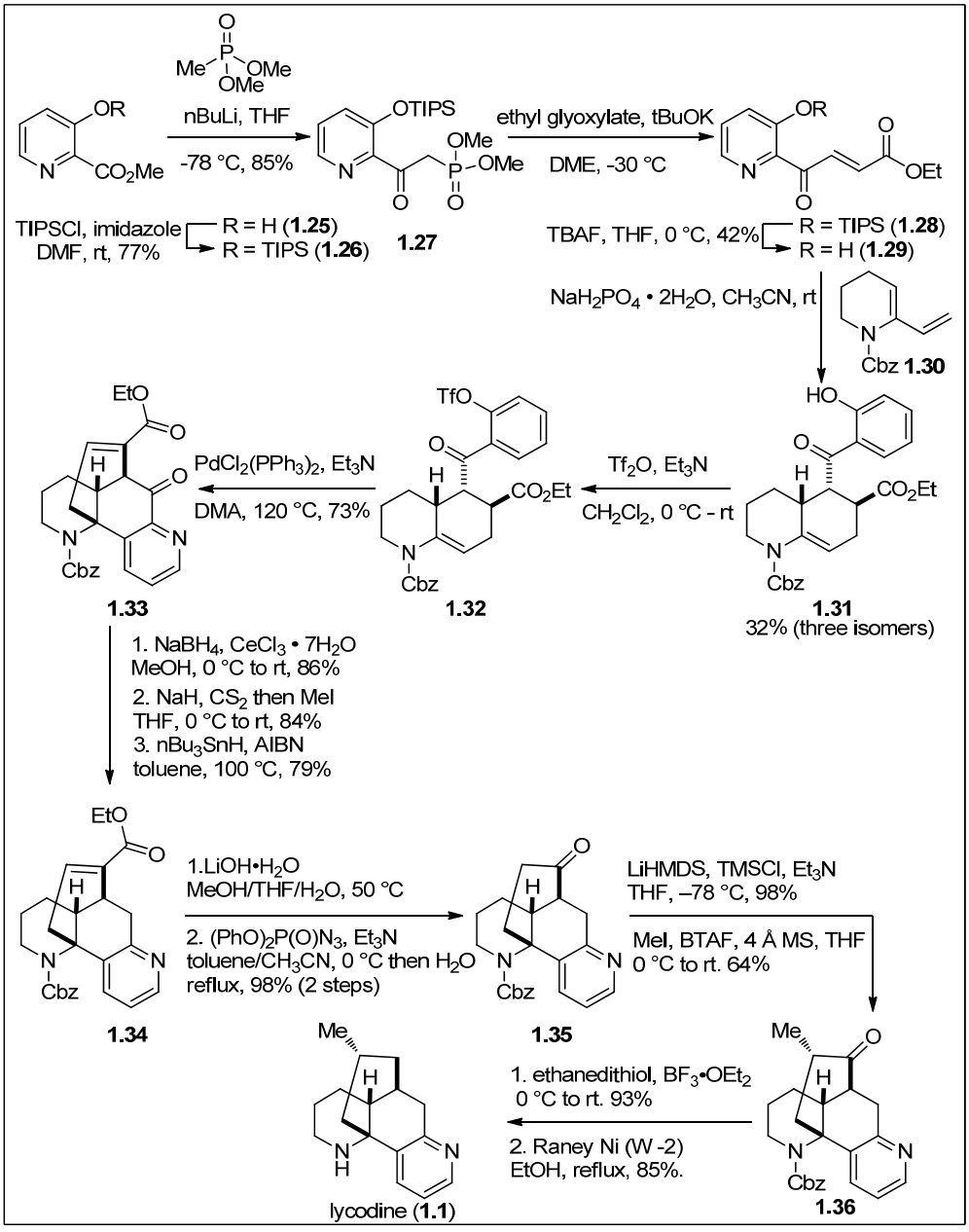
The synthesis of lycodine was achieved in racemic form twice, once by Heathcock[10] and coworkers and subsequently by Tsukano[11], Hirama and coworkers. Heathcock's synthesis (Scheme 1.1) was a landmark achievement for the time. The overall yield of lycodine **1.1** was 16% over 11 synthetic steps. The synthesis started with cyanodione **1.20** which was treated with oxalyl chloride to give a chlorocyclohexenone intermediate that was treated with a zinc-copper couple in methanol, to provide enone **1.21** on the gram scale. Conjugate addition of the anion of a hydrazone led to the diketone product **1.22**. Masking the diketone as a diacetal intermediate and reduction of the nitrile provided the corresponding amine **1.23**. Under acid deprotection **1.23**, in situ, imine formation and a tandem Mannich reaction occurred to generate ketone **1.24**. The pyridine heterocycle was then formed in four steps providing lycodine **1.1**.

Scheme 1.1 Heathcock's synthesis of (±)-lycodine.



In 2010, Tsukano and Hirama finished the second synthesis of lycodine (Scheme 1.2).[11] Key features included an intermolecular Diels-Alder cycloaddition and an intramolecular Heck reaction. The step count for the synthesis is 16 and an overall yield of 1.8%. The synthesis started from the 3-hydroxyl pyridyl ester **1.25** which was subjected to a TIPS protection to give TIPS ether **1.26**. Reaction of ester **1.26** generated phosphate **1.27**. The product **1.27** underwent a HWE reaction to provide the unsaturated ester **1.28** which was desilylated to form the hydroxyl pyridine **1.29** that was subjected to Diels-Alder reaction with **1.30**. The reaction afforded the desired compound **1.31** with additional undesired isomers. After triflation, the compound **1.32** underwent a Heck reaction to give the transannulated product **1.33**. The ester **1.34** was saponified and subjected to a Schmidt reaction and, after hydrolysis, pyridyl ketone **1.35** was formed. Lastly, methylation and reduction of the ketone through a thioacetal formed lycodine.

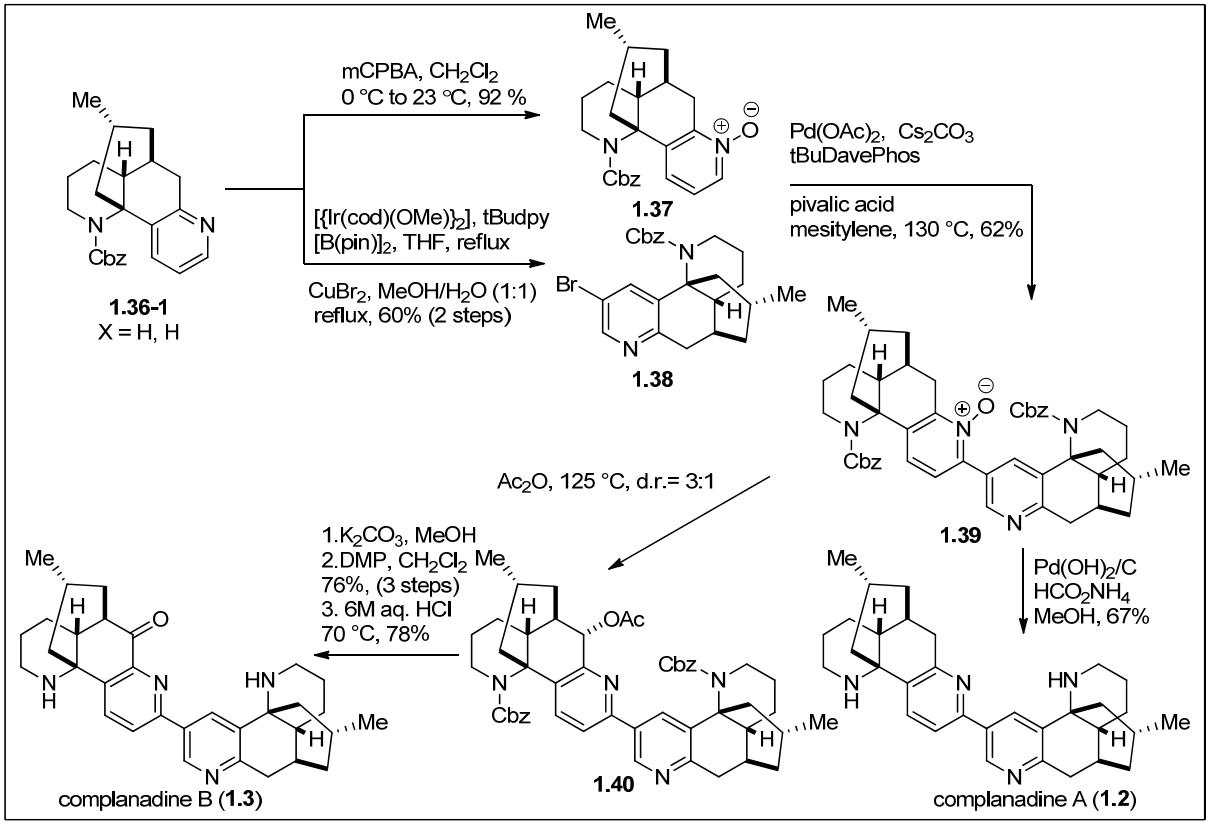
Scheme 1.2 Tsukano and Hirama's synthesis of (±)-lycodine.



1.5 Additional Syntheses of Complanadine A and Complanadine B

The Tsukano and Hirama group (Scheme 1.3) followed their synthesis of lycodine with syntheses of complanadines A and B (**1.2** and **1.3**) in 2013[11,12]. After screening they seperated the enantiomers of **1.36** by amylose chiral column to provide (+)-**1.36** and (-)-**1.36**. Oxidation of **1.36** to the pyridine N-oxide **1.37** and borylation of **1.36** under Hartwig's borolative conditions followed by conversion of boron to bromine the resulting bromide **1.38** was formed. In the key transformation a dehydrogenerative coupling reaction of **1.37** and **1.38** was achieved using palladium catalysis based on the work of Fagnou and Buchwald.[14] Complanadine A **1.2** was then formed by reduction of **1.39**. For complanadine B **1.3**, *N*-oxide intermediate **1.39** was treated with acetic anhydride to transfer the oxidation at nitrogen to the benzylic position to **1.40**. Three additional deprotection and oxidation reactions then provided complanadine B **1.3**.

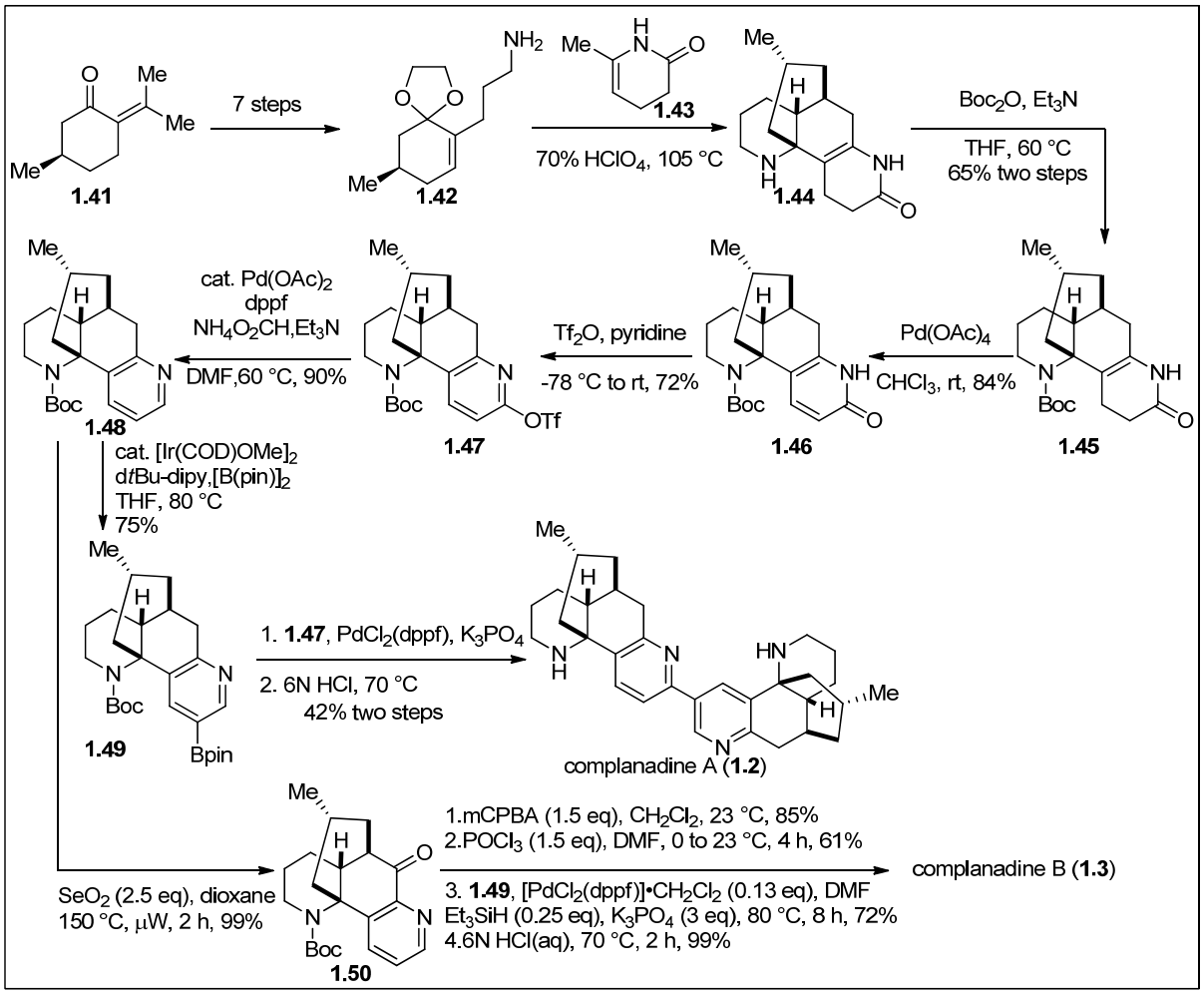
Scheme 1.3 Tsukano and Hirama's synthesis of complanadine A and complanadine B.



Sarpong's synthesis[13] (Scheme 1.4), which coincided with ours, started with the amino ketal **1.42**, generated in a seven-step procedure from pulegone **1.41**. A tandem cyclizations using enamide **1.43** and the amino ketal **1.42** formed *N*-desmethyl α-obscurine **1.44** in 70% yield on the gram scale. The Boc-protected lycodine **1.45** could be made in four steps. At this stage the application of an iridium catalyzed borylation of **1.48** genetaed borate ester **1.49**. Suzuki cross-coupling of boronic ester **1.48** and triflate **1.47** provided protected complanadine A that was deprotected by removal of the Boc protecting groups with acid to give complanadine A **1.2** in 42% yield over two steps. In the Sarpong group's synthesis of complanadine B the intermediate **1.48** was oxidized to

provide ketone **1.50** that was chlorinated at the 2-position of the pyridine and coupled to the boronate **1.49**.

Scheme 1.4: Sarpong's synthesis of complanadine A and complanadine B.



1.6 Conclusion

The background science of complanadine A and lycodine including the isolation of complanadine A **1.2** and lycodine **1.1**, biological activity of complanadine A **1.2**, the proposed biosynthesis of the lycopodium alkaloids, and the syntheses of lycodine, complanadine A **1.2** and complanadine B **1.3** were described.

1.7 References

1. (a) Ma, X.; Gang, D. R., The lycopodium alkaloids. *Natural Product Reports* **2004,** *21* (6), 752-772; (b) Ayer, W., The lycopodium alkaloids. *Nattural Product Reports* **1991,** *8* (5), 455-463; (c) Hirasawa, Y.; Kobayashi, J. i.; Morita, H., The lycopodium alkaloids. *ChemInform* **2009,** *40* (24), DOI: 10.1002/chin.200924235.

2. Anet, F.; Eves, C., Lycodine, a New Alkaloid of Lycopodium annotinum. *Canadian Journal of Chemistry* **1958,** *36* (6), 902-909.

3. Ayer, W.; Iverach, G., The Structure of Lycodine. *Canadian Journal of Chemistry* **1960,** *38* (10), 1823-1826.

4. Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H., Complanadine A, a new dimeric alkaloid from Lycopodium complanatum. *Tetrahedron Letters* **2000,** *41* (47), 9069-9073.

5. (a) Morita, H.; Ishiuchi, K. i.; Haganuma, A.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. i., Complanadine B, obscurumines A and B, new alkaloids from two species of Lycopodium. *Tetrahedron* **2005,** *61* (8), 1955-1960; (b) Ishiuchi, K. i.; Kubota, T.; Mikami, Y.; Obara, Y.; Nakahata, N.; Kobayashi, J., Complanadines C and D, new dimeric alkaloids from Lycopodium complanatum. *Bioorganic & Medicinal Chemistry* **2007,** *15* (1), 413-417; (c) Ishiuchi, K. i.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Mori, K.; Obara, Y.; Nakahata, N.; Kobayashi, J., Lyconadins D and E, and complanadine E, new Lycopodium alkaloids from Lycopodium complanatum. *Bioorganic & Medicinal Chemistry* **2011,** *19* (2), 749-753.

6. Wilson, R. M.; Danishefsky, S. J., Small Molecule Natural Products in the Discovery of Therapeutic Agents: The Synthesis Connection†. *Journal of Organic Chemistry* **2006,** *71* (22), 8329-8351.

7. (a) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H., Complanadine A, a new dimeric alkaloid from Lycopodium complanatum. *Tetrahedron Letters* **2000,** *41* (47), 9069-9073; (b) Morita, H.; Ishiuchi, K.; Haganuma, A.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J., Complanadine B, obscurumines A and B, new alkaloids from two species of Lycopodium. *Tetrahedron* **2005,** *61* (8), 1955-1960.

8. Conroy, H., Biogenesis of Lycopodium alkaloids. *Tetrahedron Letters* **1960,** *1* (31), 34-37.

9. Kitajima, M.; Takayama, H., Lycopodium Alkaloids: Isolation and Asymmetric Synthesis. *Alkaloid Synthesis* **2012**, 1-31.

10. (a) Kleinman, E.; Heathcock, C. H., Total synthesis of (±)-Lycodine. *Tetrahedron Letters* **1979,** *20* (43), 4125-4128; (b) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S., Total synthesis of lycopodium alkaloids: (±)-lycopodine, (±)-lycodine, and (±)-lycodoline. *Journal of the American Chemical Society* **1982,** *104* (4), 1054-1068.

11. Tsukano, C.; Zhao, L.; Takemoto, Y.; Hirama, M., Concise Total Synthesis of (±)-Lycodine. *European Journal of Organic Chemistry* **2010,** *2010* (22), 4198-4200.

12. Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M., Total Syntheses of Complanadines A and B. *Angewandte Chemie International Edition* **2013,** *125* (6), 1766-1769.

13. (a) Fischer, D. F.; Sarpong, R., Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C−H Functionalization. *Journal of the American Chemical Society* **2010,** *132* (17), 5926-5927; (b) Newton, J. N.; Fischer, D. F.; Sarpong, R., Synthetic Studies on Pseudo-Dimeric Lycopodium Alkaloids: Total Synthesis of Complanadine B. *Angewandte Chemie International Edition* **2013,** *52* (6), 1726-1730.

14. (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K., A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine N-Oxides. *Journal of the American Chemical Society* **2005,** *127* (51), 18020-18021; (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L., Novel Electron-Rich Bulky Phosphine Ligands Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers. *Journal of the American Chemical Society* **1999,** *121* (18), 4369-4378.

15. Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *Journal of American. Chemical Society*, **2010**, *132* (17), 5924-5925.

CHAPTER 2 Synthesis of Complanadine A and Lycodine - First and Second Generation Syntheses of Complanadine A

2.1 Retrosynthetic Analysis of Complanadine A and Lycodine

The synthesis of complanadine A[1, 2] was envisioned through the application of sequential [2+2+2] metal controlled cycloaddition reactions between a disubstituted-butadiyne **2.4** and two molecules of alkyne-nitrile **2.1** (Figure 2.1). Two potential sequences for the ordered, regioselective formation of the pyridine rings were possible, both generating complanadine A.

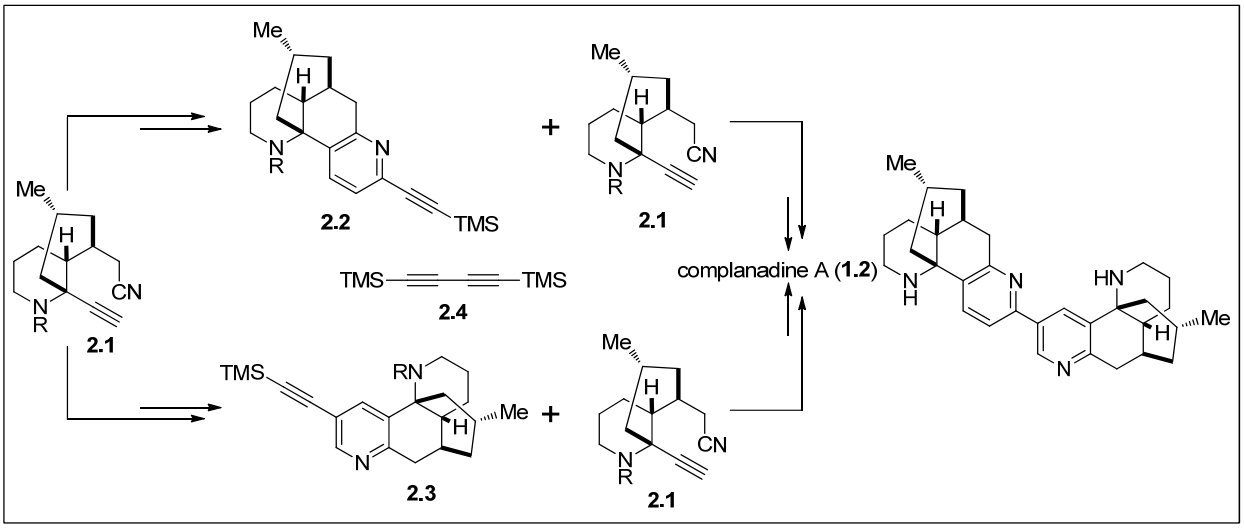


Figure 2.1. Retrosynthetic analysis of the complanadine A.

A variety of metals have been employed for pyridine synthesis using the 2+2+2 cycloaddition using one unit of a nitrile and two alkynes. The metals used for these reactions include; ruthenium[3], rhodium[4], titanium[5], tantalum[6], nickel[7], iron[8], and cobalt[9]. Cobalt represented the most promising metal as it has shown the greatest tolerance for functionality. As shown in Figure 2.2 the catalytic cycle proceedes through four steps.[10] Although the sequence appears promising there are challenges; first, as the reaction forms intermediate metallacycle such as **2.21** regioselectivity will be an issue and secondly, alkyne trimerization leading to the formation of substituted benzenes is possible.[11]

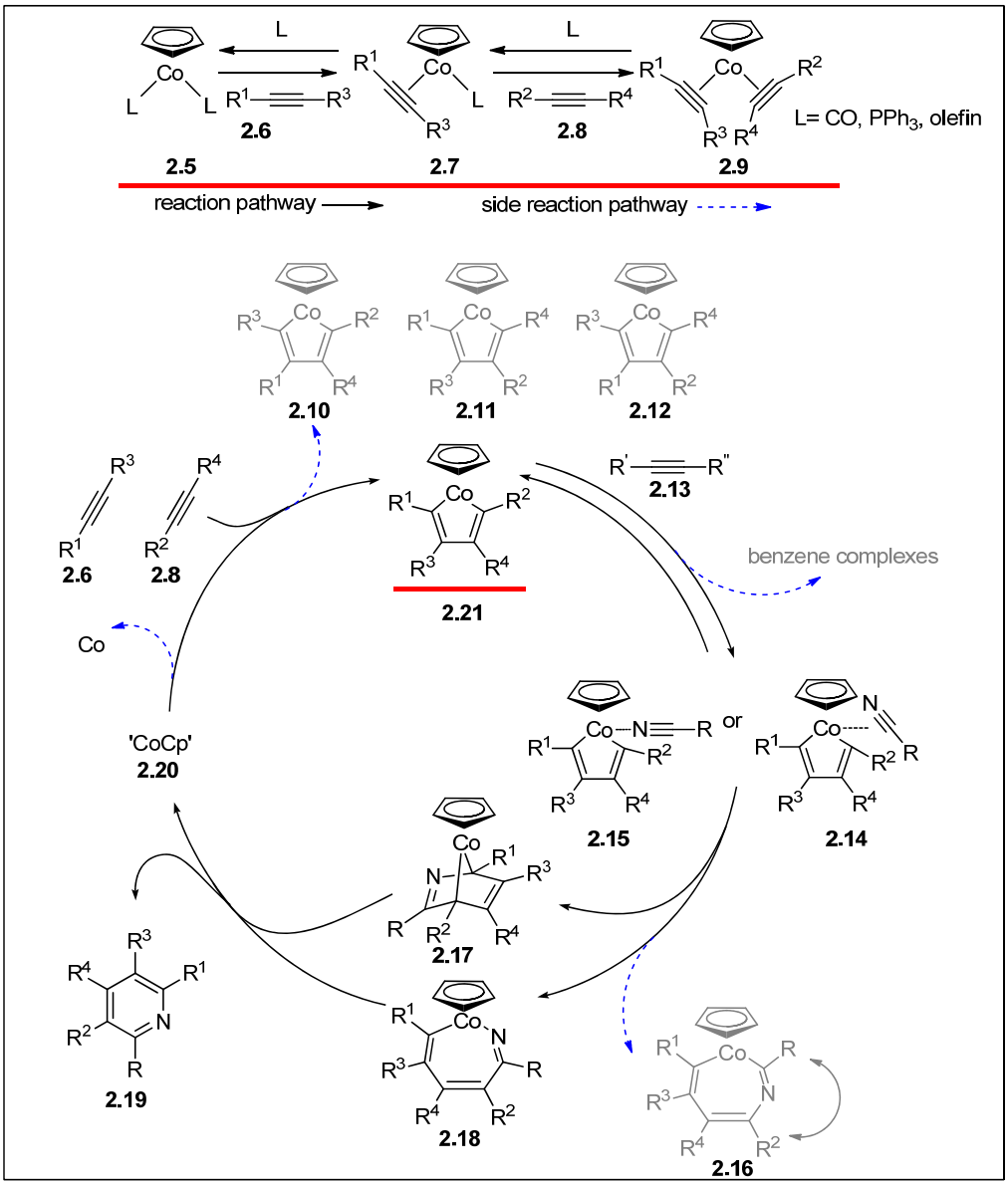


Figure 2.2. Mechanism of the cobalt-mediated [2+2+2] reaction to form pyridines.

2.2 Synthesis of Alkynyl Nitriles Bicyclic Compound

We chose natural (+)-pulegone **2.27** as the starting material for the synthesis due to its cost and availability with the correct sterochemical configuration (Figure 2.3). This chiral center was envisioned to allow all of the other stereocenters to form, in a diastereoselective manner, based on this initial stereocenter. Additionally the compound can be readily transformed into a number of useful compounds including thioether **2.26**.

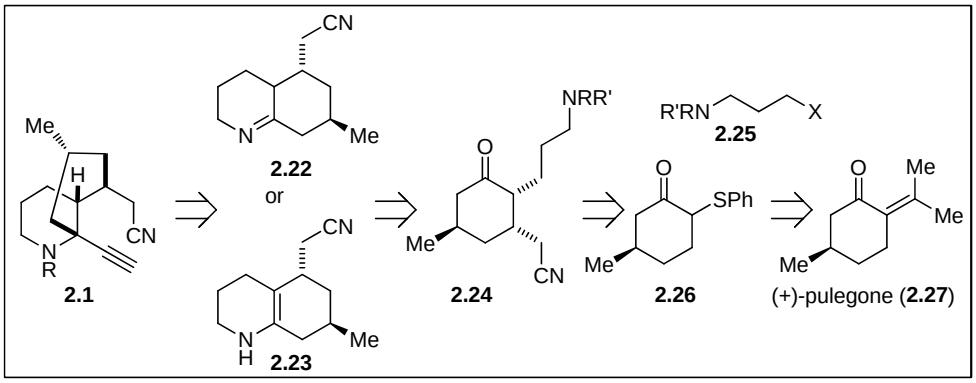
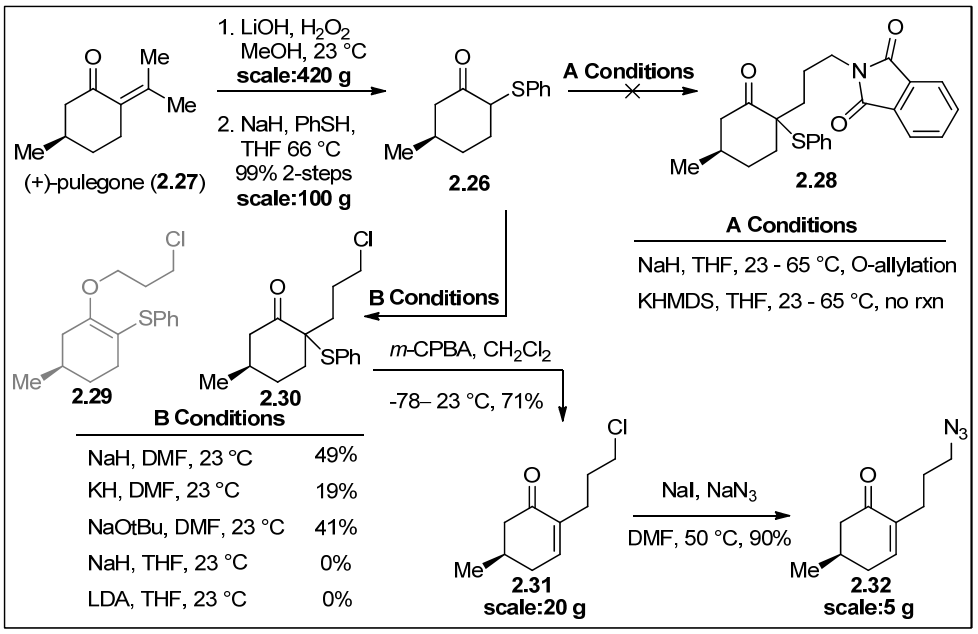


Figure 2.3. Second general retrosynthetic route to bicyclic compound **2.1**.

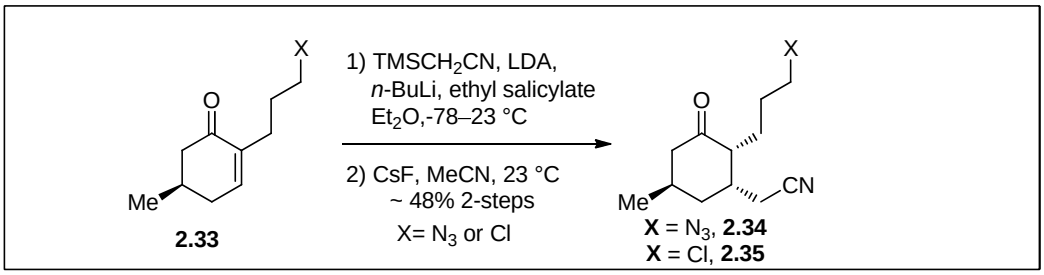
Following from literature precedence thioether **2.26** was synthesized on batches of more than 100g.[12] Alkylation of thioether **2.26** using sodium hydride and a phthamidyl iodide afforded exclusively the O-alkylation product (Scheme 2.1). Use of 3-chloro-1-iodo-propane, however, provided the C-alkylation product **2.30** in acceptable yield. The solvent for this reaction proved critical as THF was less efficient DMF. In the next step, a Finkelstein reaction using sodium iodide and sodium azide provided the alkyl azide compound **2.32** in 90% yield.

Scheme 2.1. Synthesis of enone azide **2.32**.



The use of the anion of $TMSCH_2CN$, generated by deprotonation using LDA, in a Michael addition generated the desired adduct **2.33** (Scheme 2.2). This reaction had a competing Peterson olefination. To minimize the formation of the *trans* isomer ethyl salicylate was used for protonation[13] of the resulting enolate, delivering the proton on the opposite face of the TMS acetonitrile group to afford **2.34** or **2.35** in 48% yield after a cesium fluoride desilylation.

Scheme 2.2. Michael additions condition optimization.



We planned to synthesize the quaternary center of **2.1** through an intramolecular displacement as shown in Figure 2.4.

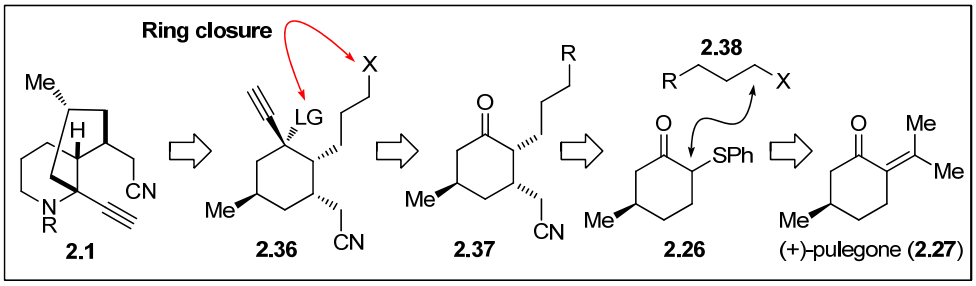
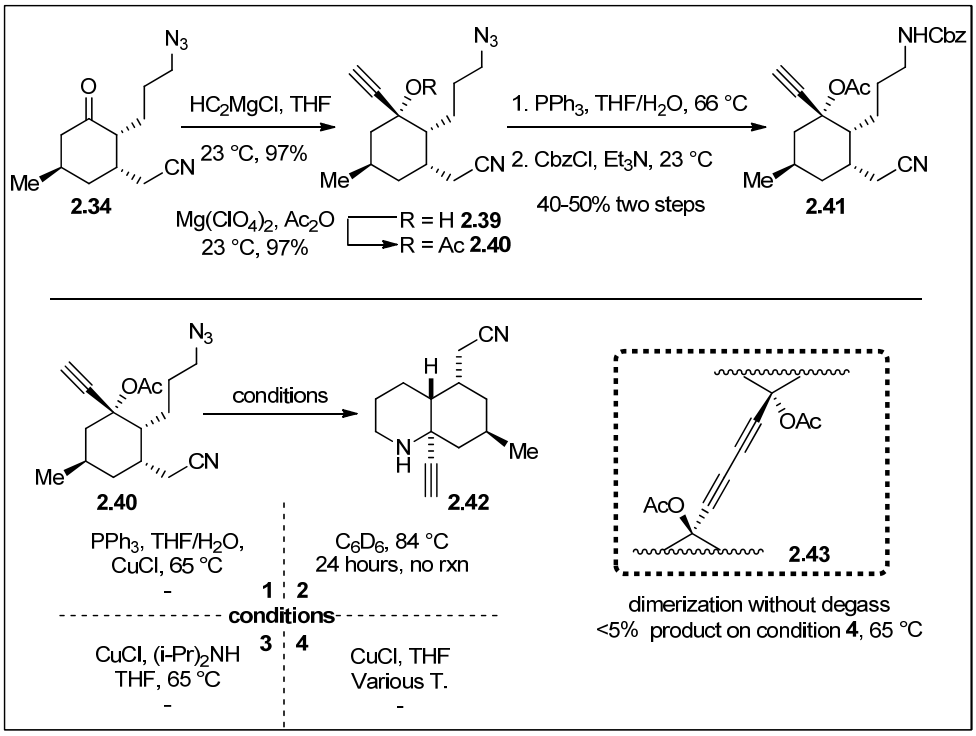


Figure 2.4. Retrosynthetic approach to the bicyclic compound **2.1**.

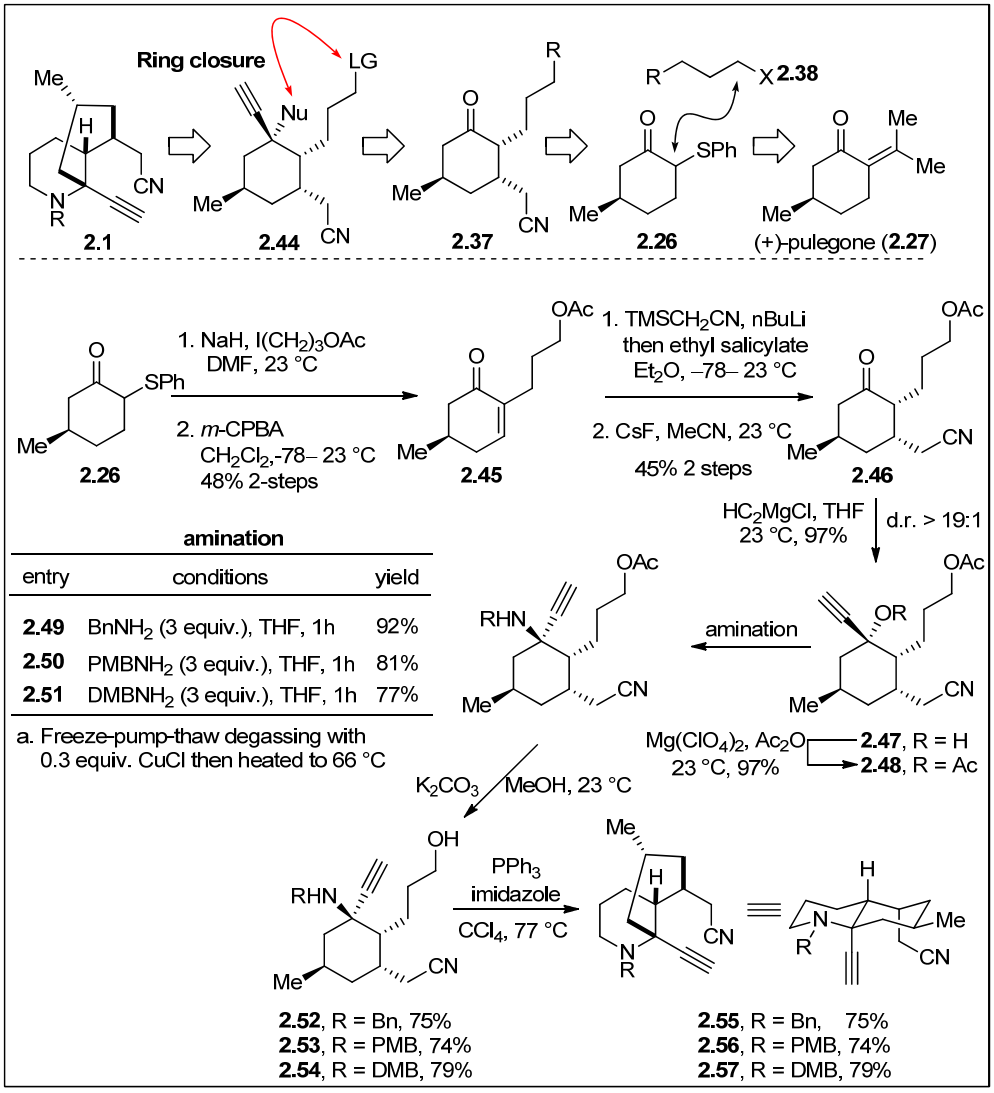
The azido ketone **2.34** was reacted with ethynyl Grignard reagents to generate the corresponding propargyl alcohol (Scheme 2.3). To a solution of the resulting propargyl alcohol **2.39** the hydroxyl group was converted to an acetate using catalytic magnesium perchlorate in neat acetic anhydride. A Staudinger reaction was then used to reduce **2.40** to the amine which was protected with Cbz group to form **2.41** in moderate yield. Cyclization through a copper catalyzed amide addition to the propargyl acetate failed.[14] Therefore, we attempted an intermolecular displacement using benzyl amines.

Scheme 2.3. Failed attempts to synthesize alkyne-nitrile bicyclic compound.



Followed our existing route the propargyl acetate **2.48** was prepared for the intermolecular amination reaction. Following careful degassing of the solution the copper catalyzed reaction successfully generated the desired propargyl amine (Scheme 2.4). Use of a methanolic solution of the potassium carbonate was used to deprotect the acetate, forming amino alcohol **2.49**. This compound was cyclized using triphenylphosphine and carbontetrachloride to give the desired bicyclic compound **2.55**.[15] Under the same conditions the PMB and DMB derivatives were similarly prepared.

Scheme 2.4. Successful route to the bicylic compounds **2.55**, **2.56** and **2.57**.

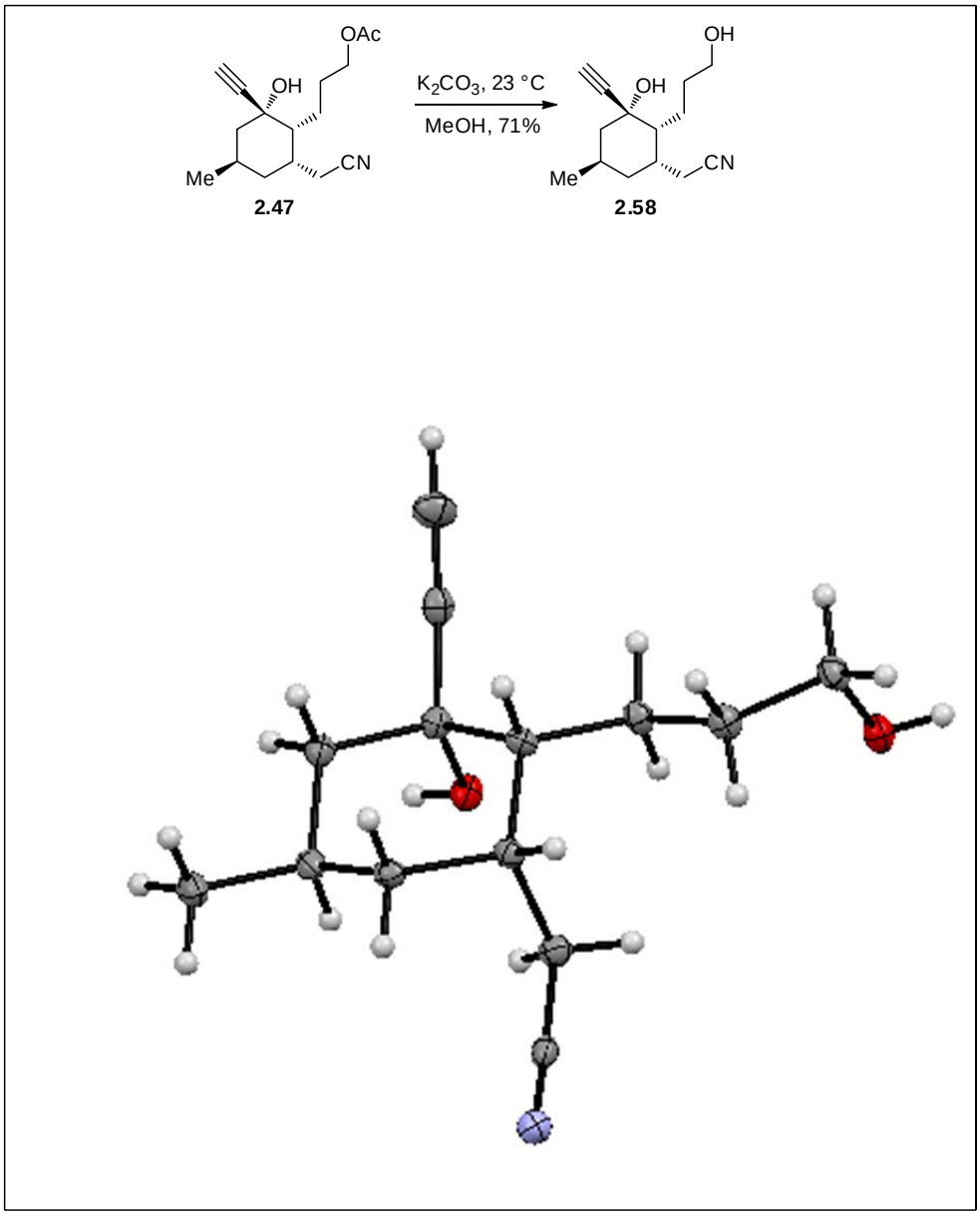


amination

entry	conditions	yield
2.49	$BnNH_2$ (3 equiv.), THF, 1h	92%
2.50	$PMBNH_2$ (3 equiv.), THF, 1h	81%
2.51	$DMBNH_2$ (3 equiv.), THF, 1h	77%

a. Freeze-pump-thaw degassing with 0.3 equiv. CuCl then heated to 66 °C

Scheme 2.5. The crystal structure of **2.58** verifying the structure.



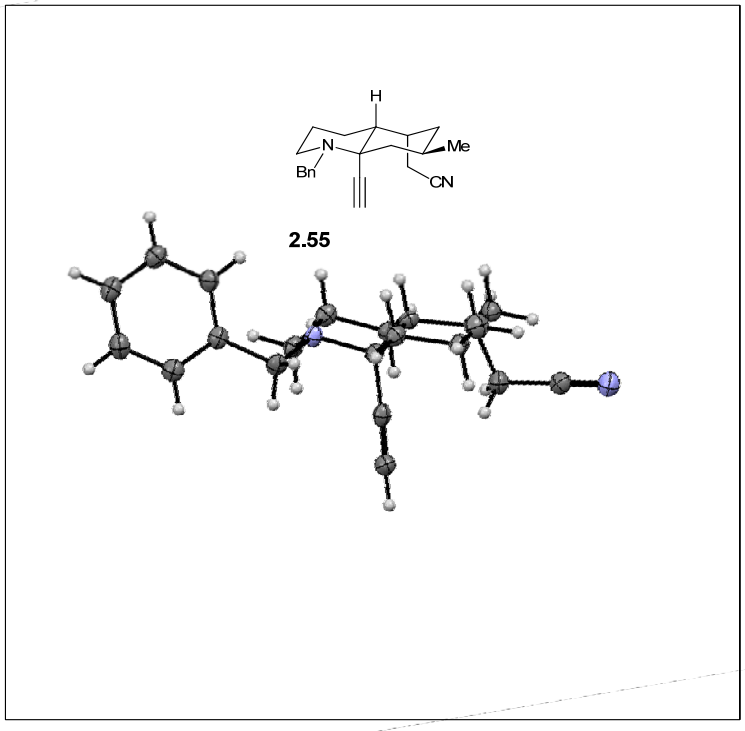


Figure 2.5. X-ray structure of the bicyclic compound **2.55**

The synthesis of the key alkyne-nitrile was achieved in an overall yield of 9 percent and provided the bicyclic compounds in three grams batches (Figure 2.6).

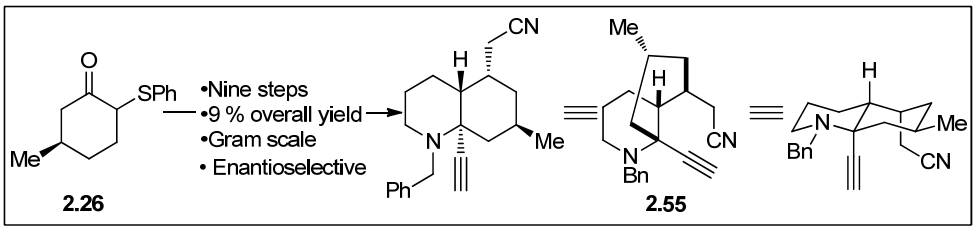
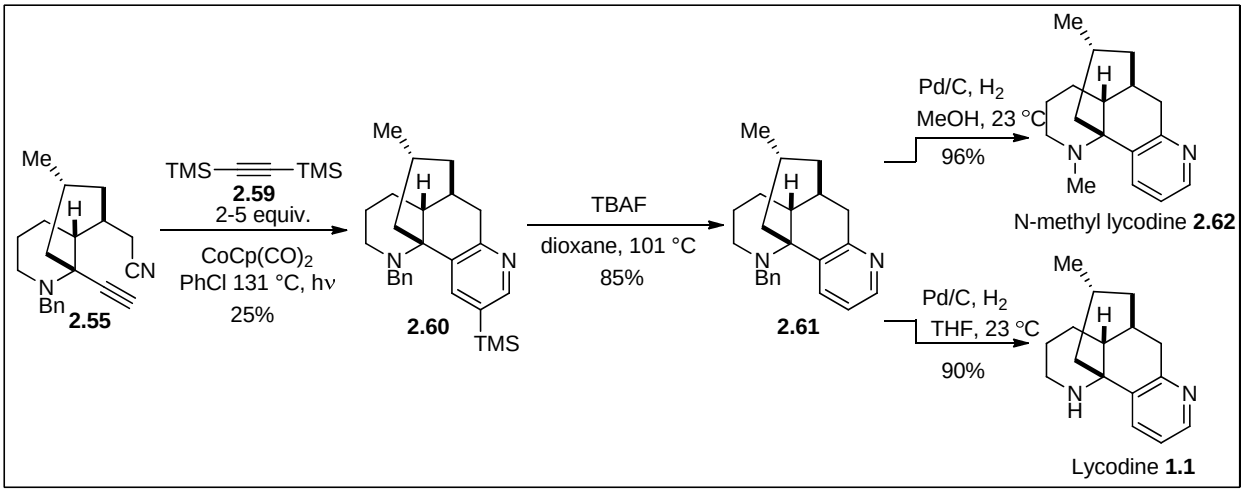


Figure 2.6. Summary of the synthesis of bicyclic compound **2.55**.

2.3 Synthesis of Lycodine and First Generation of Synthesis of Complanadine A

After minor optimization bis(trimethylsilyl)acetylene reacted with the alkyne nitrile **2.55** to generate lycodine in protected form. This compound was deprotected by TBAF desilylation of the pyridyl TMS followed by hydrogenation to remove the benzyl ether. This provided the third synthesis of lycodine to date (Scheme 2.6).

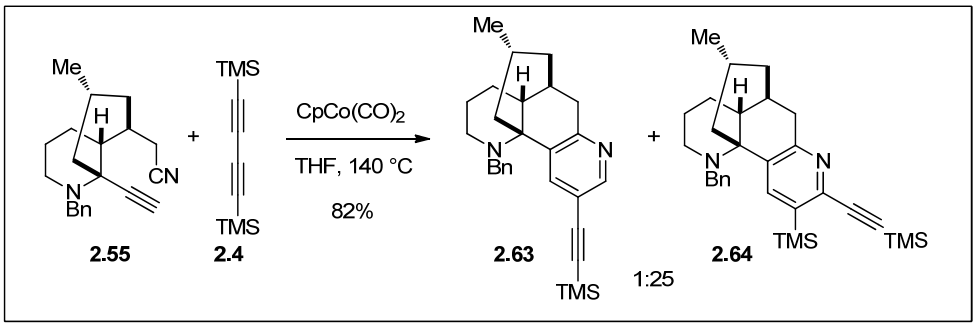
Scheme 2.6. $CpCo(CO)_2$ mediated [2+2+2] cyclcoaddition with bis(trimethyl)acetylene and the bicyclic compound and synthesis of lycodine.



After a number of experiments with butadiynes we used a modification of the cobalt catalyzed reaction developed by Schreiber and coworkers using THF at elevated temperature, with **2.55** and **2.4** to form the desired pyridine alkyne adduct in 82% yield (Scheme 2.15).[17] It was worth noting that the THF conditions were carried out on the gram scale affording, in addition to the major isomer, the minor regioisomer **2.63** on the milligram scale. In Figure 2.7 two proposals are presented for the formation of the metallocycle, one following from a steric

model put forth by Wakatsuki[9a] and another following an electronic model described by Saá and Vollhardt.[10b] The $CpCo(CO)_2$ after loss of carbon monoxide possesses a free coordination site for bistrimethylsilylbutdiyne to form complex **2.70** or **2.71**. After losing another molecule of CO and complexation bicyclic compound **2.55** with formation of mettalocycles **2.74** and **2.75** (Figure 2.8).

Scheme 2.7. THF 140 °C condition to construct pyridyl alkyne compound **2.63** and **2.64**.



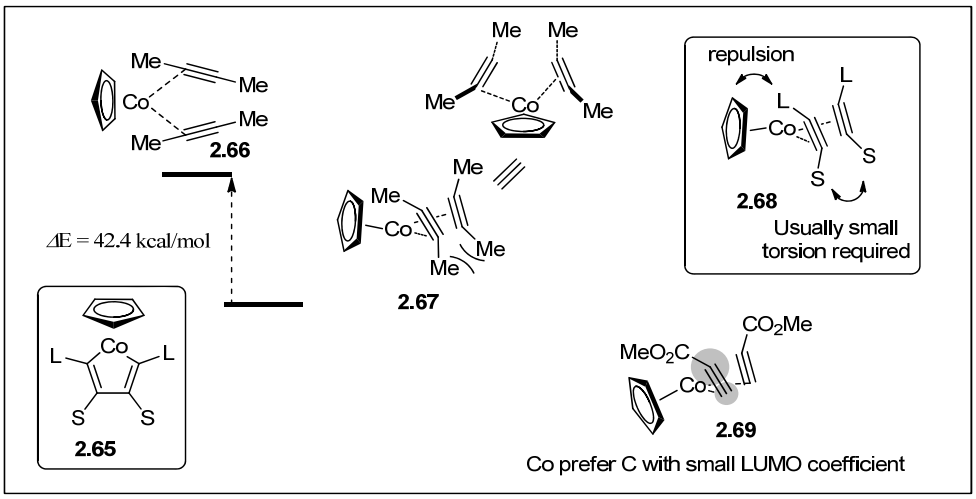


Figure. 2.7. Electronic origin for the regioselectivity of cobalt catalyzed [2+2+2] cycloaddition.

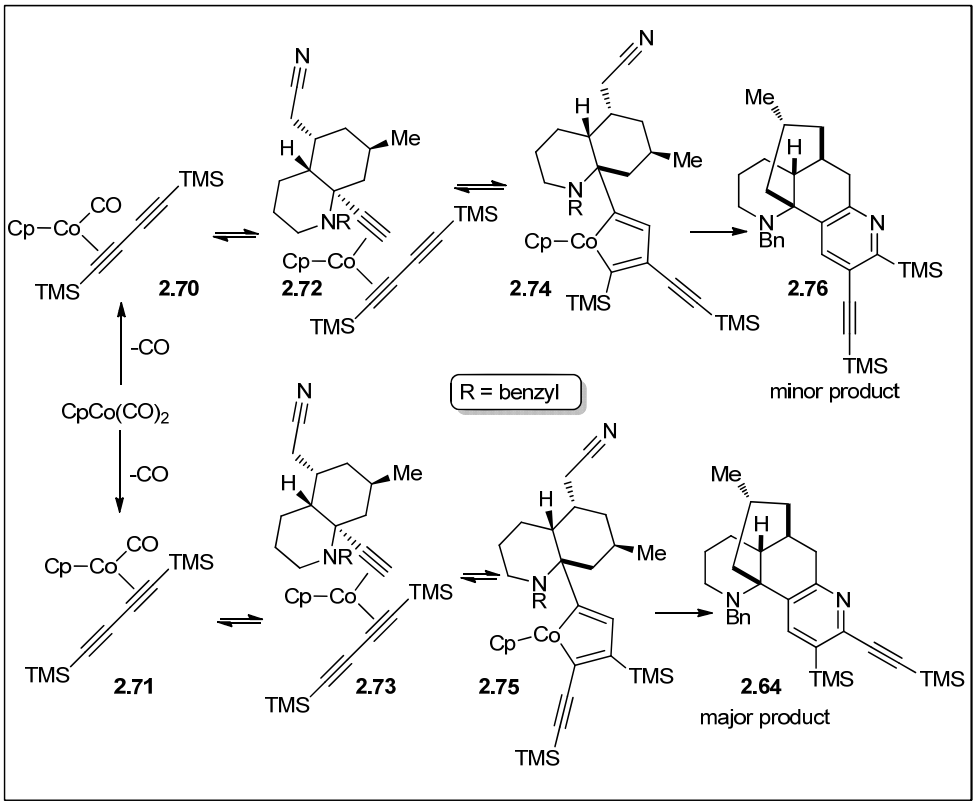
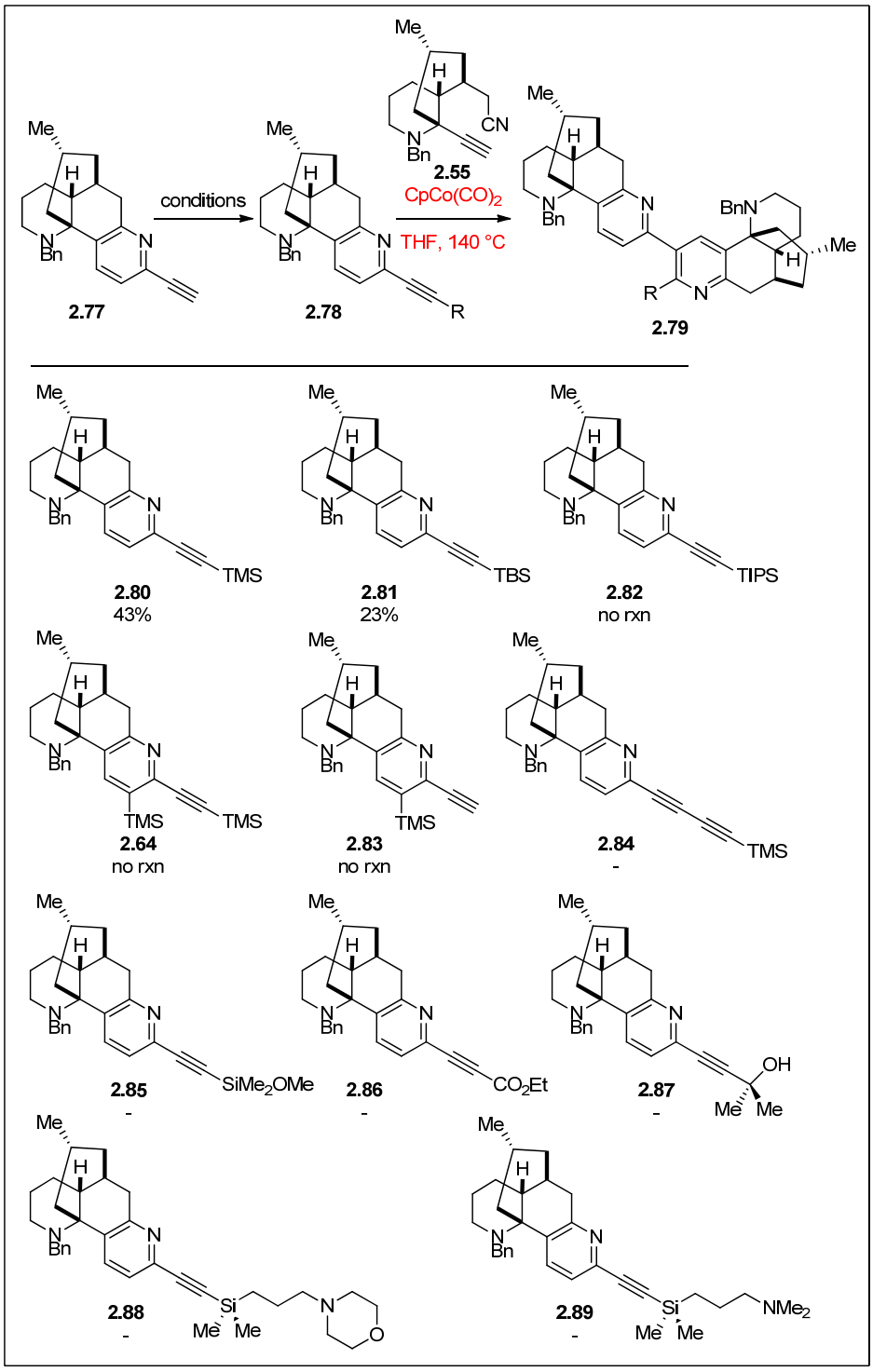


Figure 2.8. Proposed mechanism for the regioselectivity in the first [2+2+2] pyridine formation.

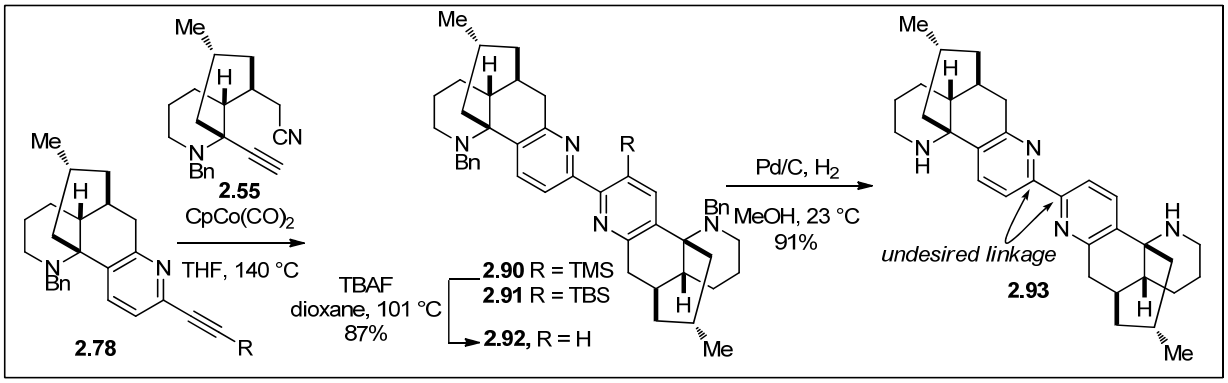
Unfortunately the second 2+2+2 cycloaddition could not be achieved directly after the first. The inability of pyridyl-alkyne **2.78** to undergo a second [2+2+2] cycloaddition was thought to be due to the steric impediment caused by the aryl-trimethylsilyl group adjacent to the alkyne. Removal of both trimethylsilyl groups with TBAF in THF generated alkyne **2.77** which was silylated using LDA and TMSCl to generate silyl-alkyne **2.88**. In addition, a series of other pyridyl-alkynes **2.64-2.89** were similarly prepared via deprotonation of **2.64** with LDA and reaction of the resulting acetylide anion with the appropriate electrophile (Scheme 2.8). These disubstituted alkynes allowed the examination of their propensity to undergo the second [2+2+2] cycloaddition.

Scheme 2.8. Utilizing THF 140 °C condition for the second [2+2+2] pyridine formation.

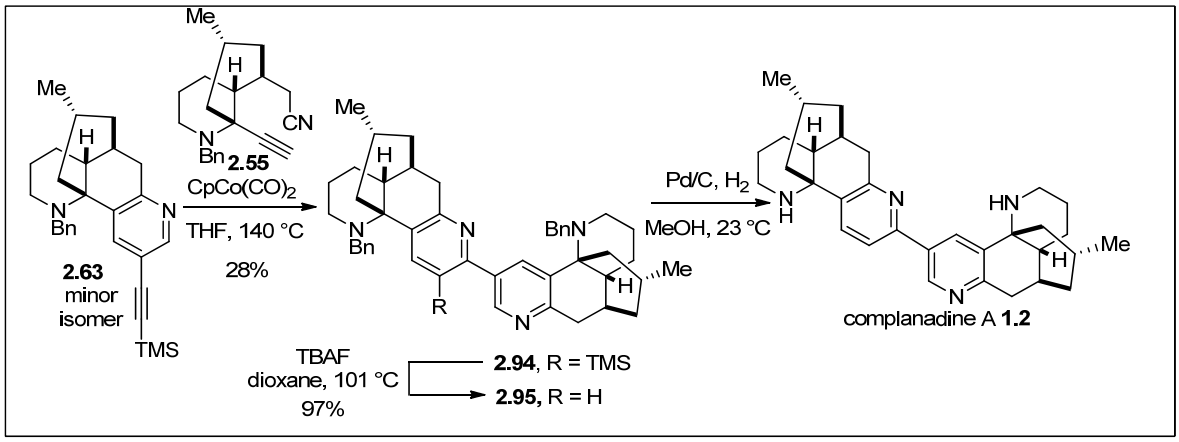


It was found that all of the reactions generated symmetric compounds such as **2.90** and **2.91** and when the aryl silicon groups were removed the simplified spectrum of symmetric compound **2.92** made it readily evident (Scheme 2.9). Furthermore removal of the benzyl group to form **2.93** additionally confirmed the assignment, supporting the conclusion that we had formed an isomer of complanadine A. However, when subjected to the same reaction conditions the minor regioisomer **2.63** did provide the desired product (Scheme 2.10). However, the low yileds associated with accessing the minor regioisomer **2.63** limited the usefulness of this approach.

Scheme 2.9. Synthesis of the undesired symmetric dimeric compound **2.93**.

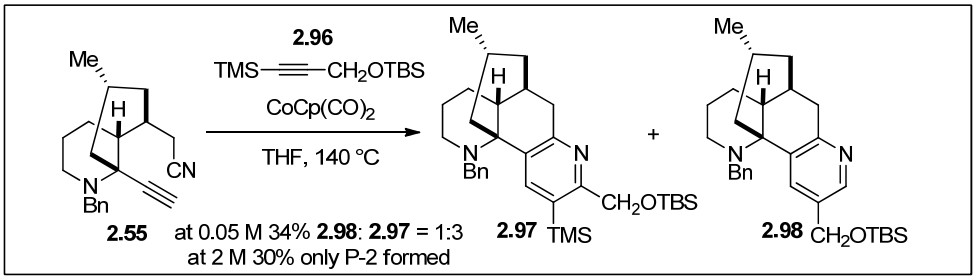


Scheme 2.10. Synthesis of complanadine A through the minor regioisomer.

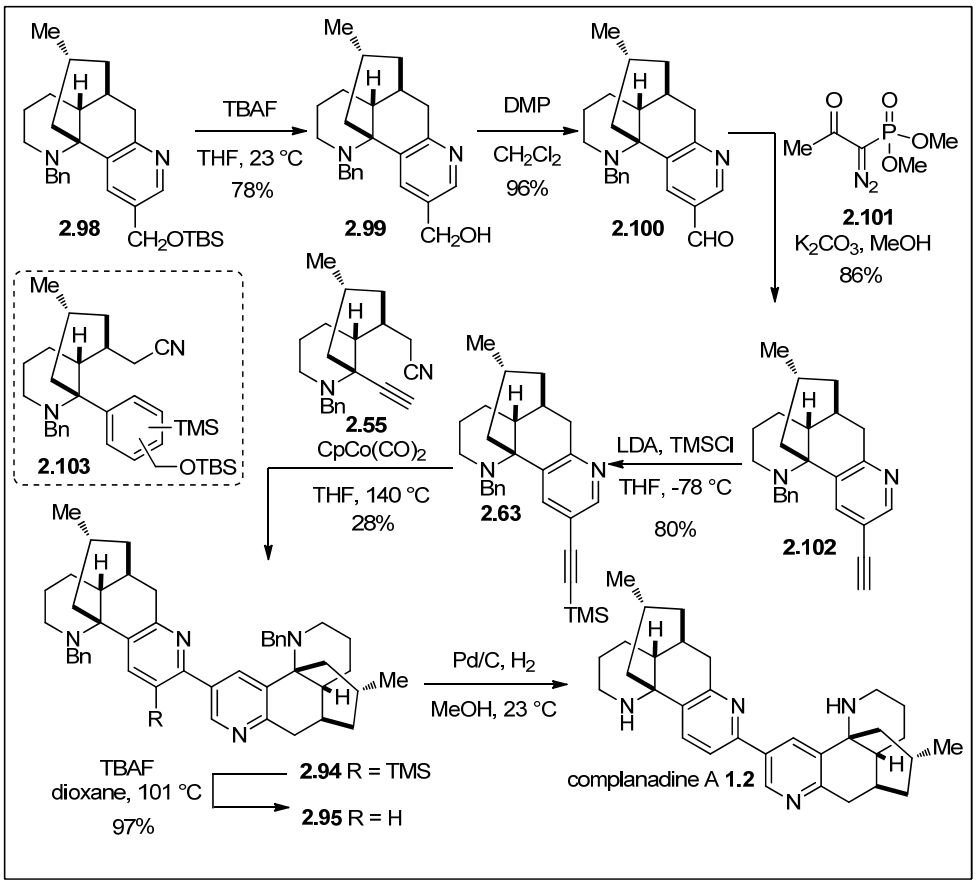


An alternative synthesis of alkyne **2.95** was achieved as outlined in Scheme 2.11. Using the [2+2+2] cycloaddition adduct **2.98** to access the propargyl ether (Scheme 2.12). The silyl ether **2.98** was transformed using standard chemistry to the desired pyridyl alkyne **2.63**. With scalable access to **2.63** the second cobalt mediated [2+2+2] reaction was achieved and complanadine A was accessed again. However, this route suffered from low yields and an increased number of steps.

Scheme 2.11. Preparation of the pyridine **2.98**.



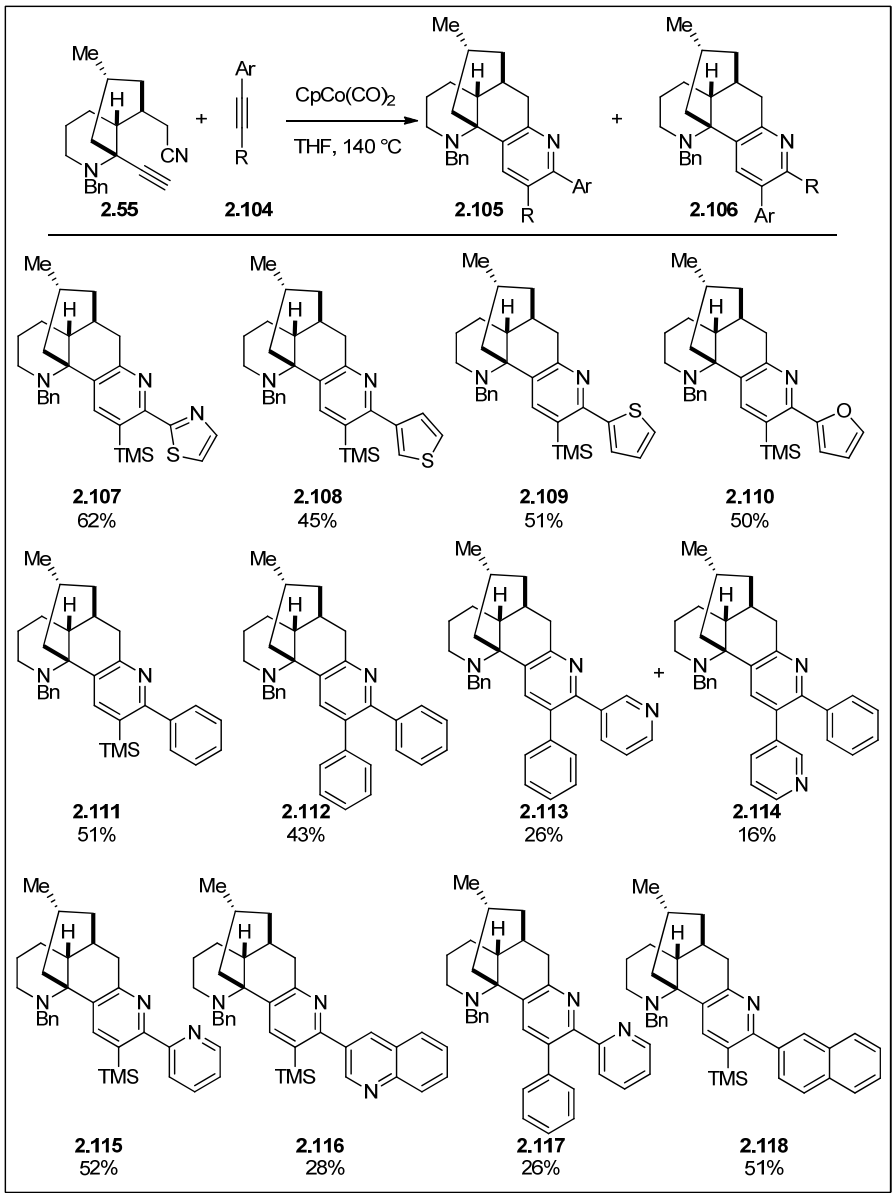
Scheme 2.12. Improved first generation of synthesis for complanadine A.



2.4 Second Generation of Synthesis of Complanadine A

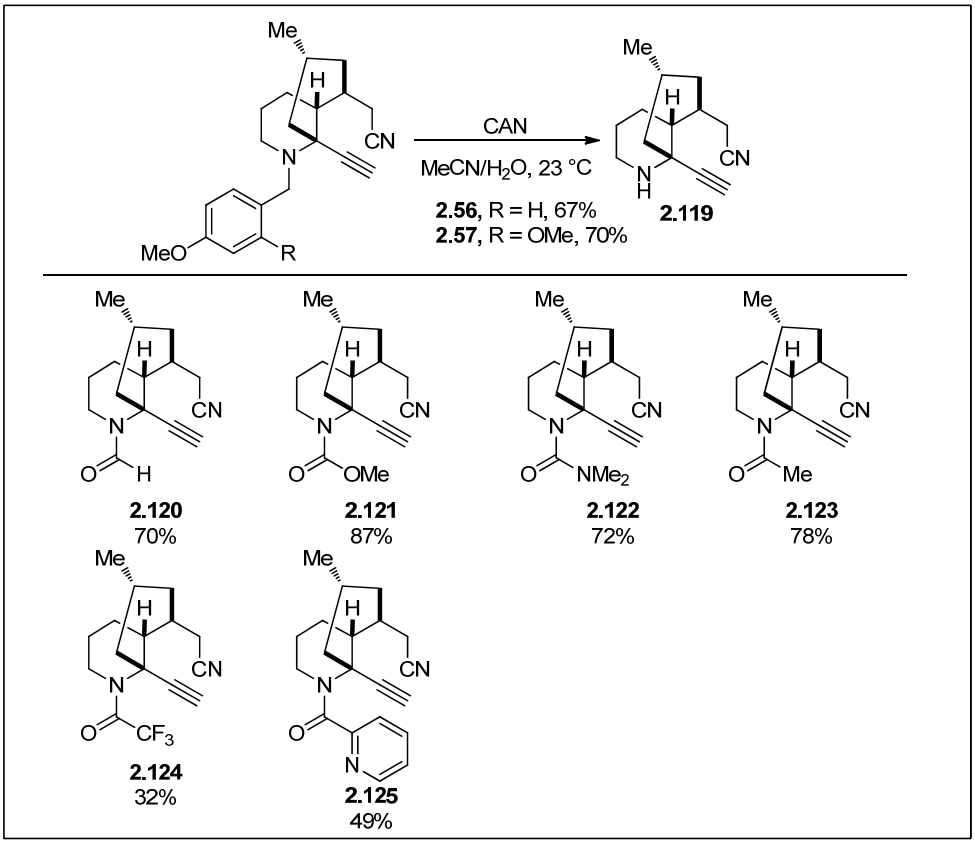
As the first [2+2+2] provided the 2-alkynylpyridine **2.64** in good yield efforts were made to utilize this compound by changing the regioselectivity of the second [2+2+2] cycloaddition. Examination of a number of alkynyl arenes revealed a strong regioselectivity preference for the reaction (Scheme 2.13).

Scheme 2.13. Cycloadditions with aryl alkynes and bicyclic compound **2.55**.



With ample quantities of the key bicyclic compound **2.55** the benzyl group was changed in an attempted to change the regioselectivity of the second [2+2+2] cycloaddition reaction. The use of CAN to cleavage the PMB group of **2.56** or DMB on **2.57** succeeded, generating the secondary amine **2.119** on the gram scale allowing the syntheses of a variety of alkyne-nitriles with different carbonyl groups (Scheme 2.14).

Scheme 2.14. Synthesis of bicyclic compound derivatives.



Using **2.120** and **2.122** under the standard THF 140 °C cobalt mediated conditions the desired isomers were formed, albeit as minor constituents (Figure 2.15). Additionally, the use of Lewis basic ligands was also found to be beneficial (Table 2.1). Additional testing of solvent, temperature, and concentration gave us an approximate set of conditions to form the desired bipyridyl **2.128** as the major product.

Scheme 2.15. The effects of the nitrogen bound functionality on the regioselectivity.

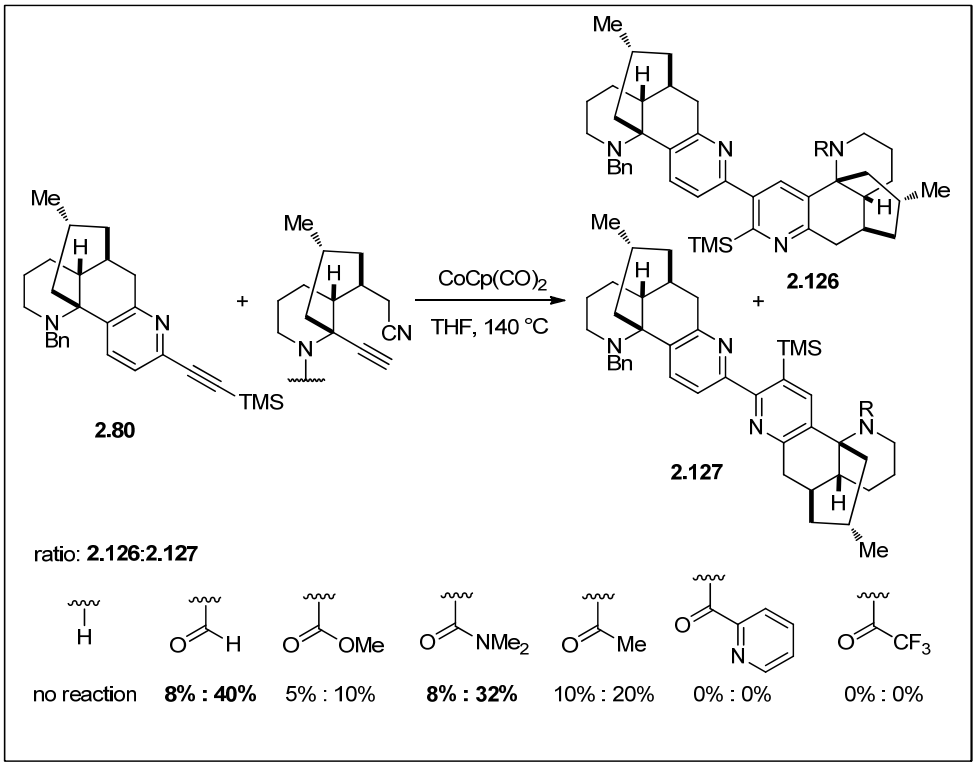
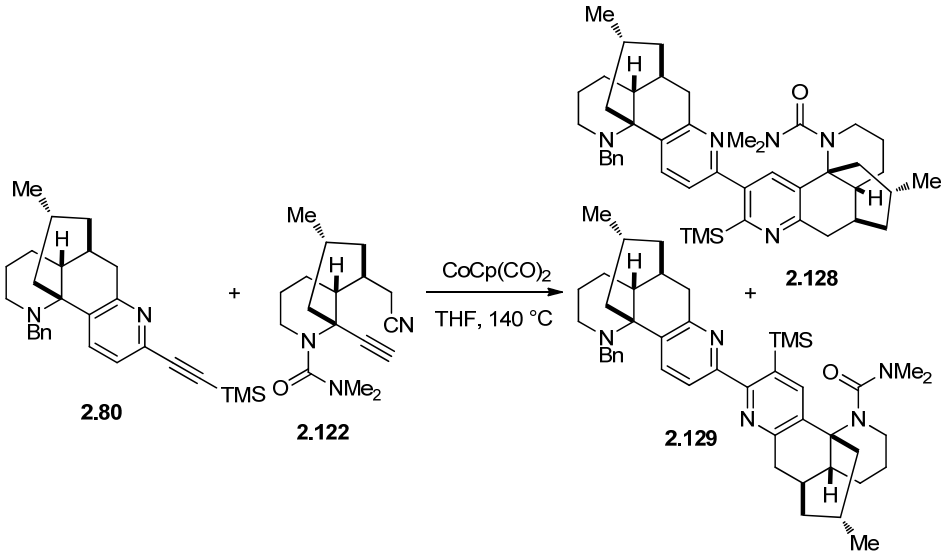
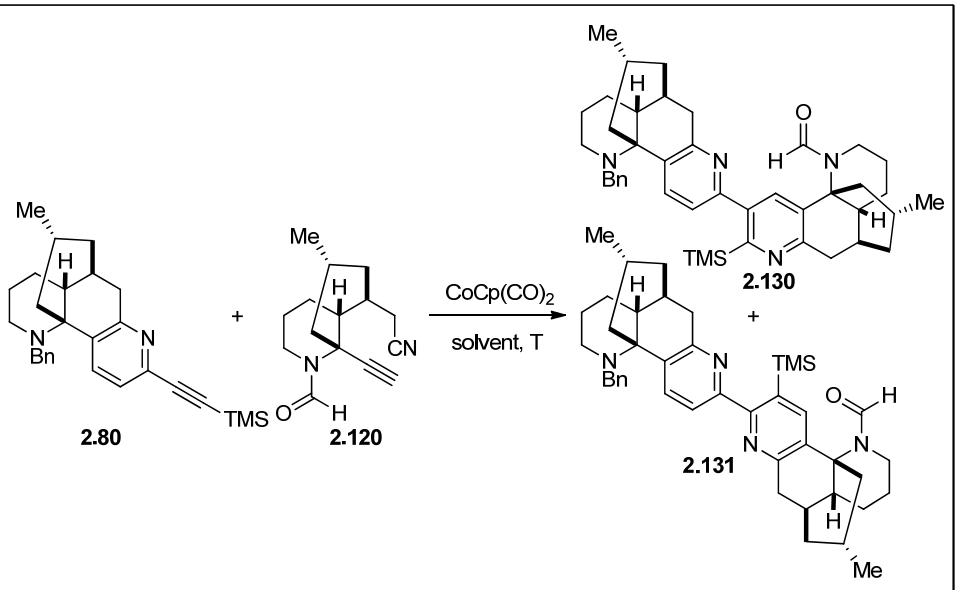


Table 2.1. The effects of additives on the second [2+2+2] cycloaddition.



additive	ratio	yield	additive	ratio	yield
no additive	1:4	40%	$AsPh_3$	1:1.3	35%
NMO	1:1.4	23%	$P(o\text{-toluyl})_3$	1:2	32%
DMAP	1.5:1	20%	DPPE	-	0%
PPh_3	1.1:1	36%	$P(2\text{-furyl})_3$	-	0%

Table 2.2. Screen of solvent, temperature and concentrations for the second [2+2+2] cycloaddition.



Solvent	ratio	yield
THF	5:1	40%
dioxane	3:1	46%
xylene	>20:1	38%
decane	>20:1	44%
MeOH	desilylation	-
DME	>20:1	23%
NMP	decompose	-
dioxane	1:1 (with PPh_3)	40%

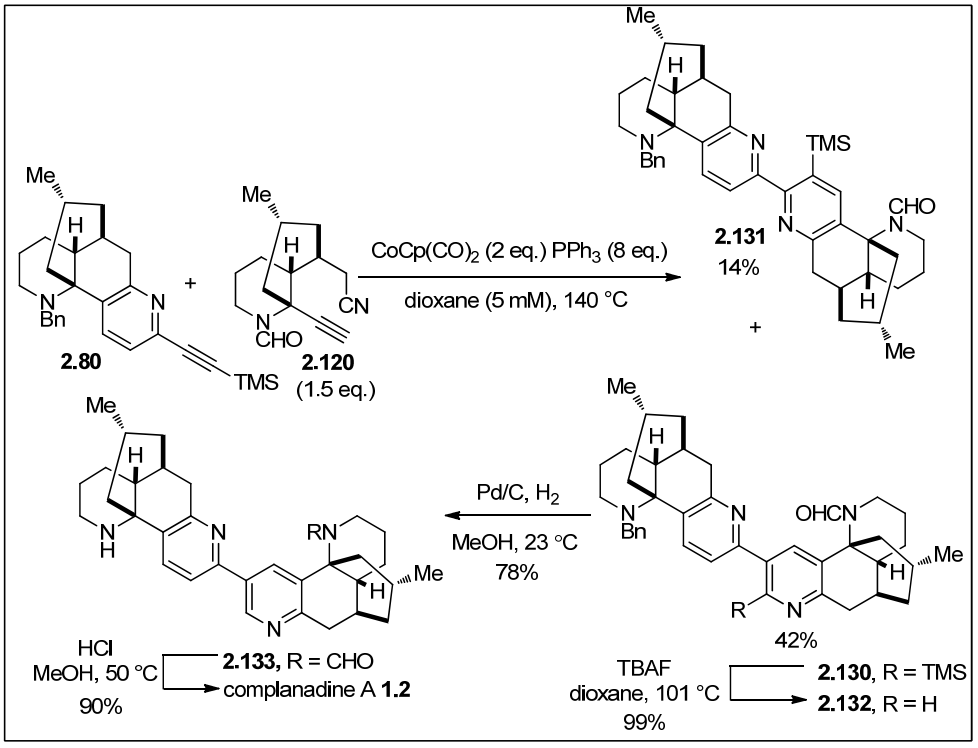
T = 140 °C

T/concentration	ratio	yield
140 °C (10 mM)	1.25:1	30%
160 °C (10 mM)	1:1	20%
120 °C (10 mM)	-	<10%
140 °C (0.1 M)	1:1	10%
140 °C (0.05 M)	1.5:1	25%
140 °C (5 mM)	2:1	45%

Sol = dioxane

The final conditions were a diluted solution of the two components and cobalt reagent in dioxane with PPh_3 heated to 140 °C to give the bipyridyl product **2.130** in 42% yield (Table 2.2). Deprotection of all of the formyl, benzyl, and silyl groups preceded over three steps to yield complanadine A (Scheme 2.16). The reversal of the regioselectivity through the use of triphenylphosphine is rationalized in Figure 2.9, due to both the sterics of triphenylphosphine and the removal of a coordination site that the pyridine could complex.

Scheme 2.16. Second generation of synthesis of complanadine A.



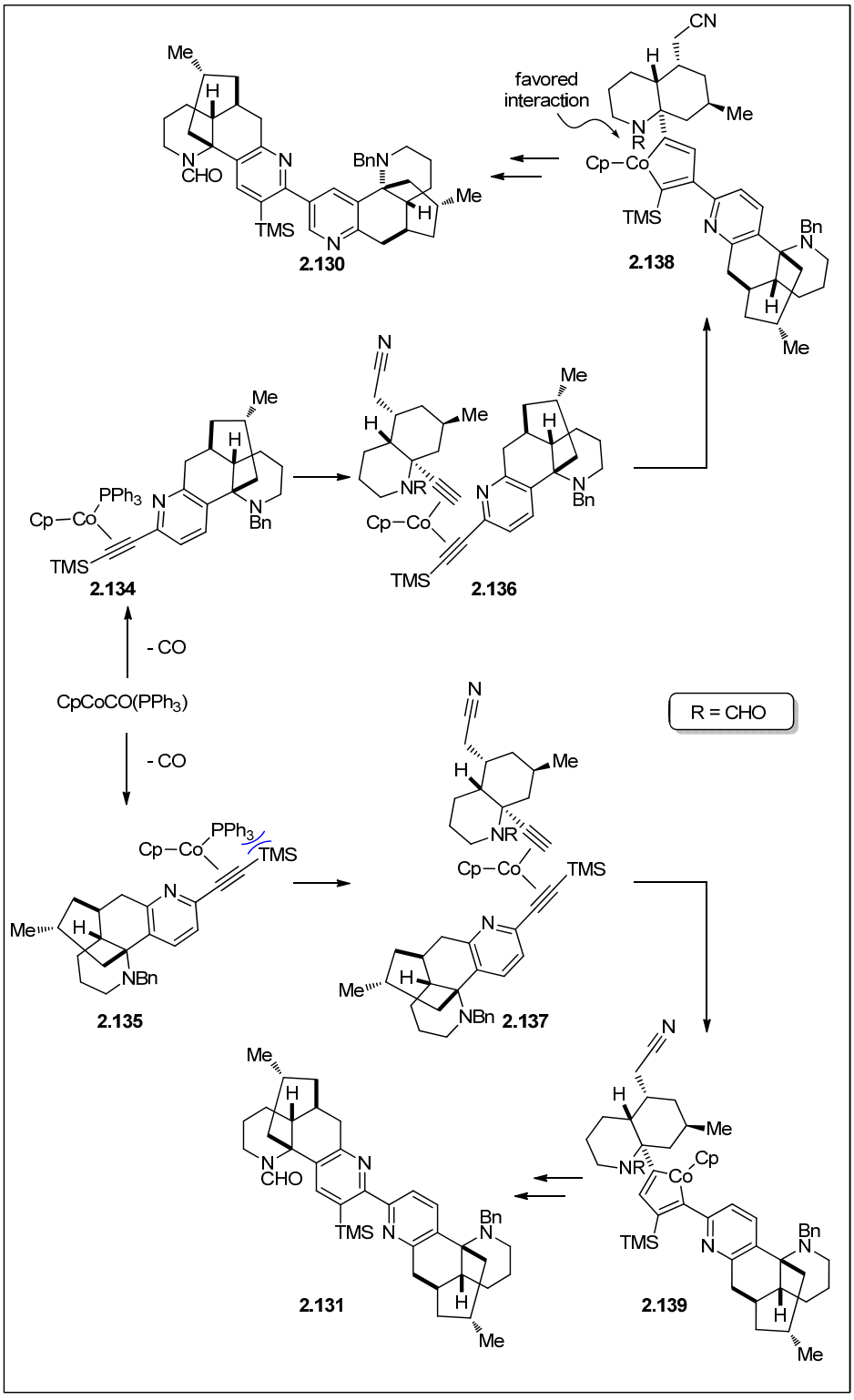


Figure 2.9. Proposed mechanism for the cobalt mediated [2+2+2] cycloaddition with PPh_3.

2.5 Conclusion

The successful syntheses of lycodine (**1.1**) and complanadine A (**1.2**), which was achieved through two separate routes, have been achieved. Both routes to complanadine A were developed utilizing cobalt-mediated [2+2+2] cycloaddition reactions. In addition, related lycodine derivatives can be rapidly accessed through similar cycloadditions using disubstituted alkynes. The controlled formation of the 2, 3'-bipyridyl core was achieved through either modifying the partners in the reaction sequence or through the use of Lewis-basic additives.

2.6 References

1. (a) Fischer, D. F.; Sarpong, R., Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C−H Functionalization. *Journal of the American Chemical Society* **2010,** *132* (17), 5926-5927; (b) Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M., Total Syntheses of Complanadines A and B. *Angewandte Chemie International Edition* **2013,** *52* (6), 1722-1725.(c) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *Journal of American. Chemical Society*, **2010**, *132* (17), 5924-5925.

2. Newton, J. N.; Fischer, D. F.; Sarpong, R., Synthetic Studies on Pseudo-Dimeric Lycopodium Alkaloids: Total Synthesis of Complanadine B. *Angewandte Chemie International Edition* **2013,** *52* (6), 1726-1730.

3. (a) Yamamoto, Y.; Ogawa, R.; Itoh, K., Significant Chemo- and Regioselectivies in the Ru(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Dicyanides. *Journal of the American Chemical Society* **2001,** *123* (25), 6189-6190; (b) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K., Ruthenium-Catalyzed Cycloaddition of 1,6-Diynes and Nitriles under Mild Conditions: Role of the Coordinating Group of Nitriles. *Chemistry – A European Journal* **2006,** *12* (21), 5618-5631.

4. (a) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P., Rhodium-catalyzed synthesis of pyridines from alkynes and nitriles. *Journal of Molecular Catalysis* **1987,** *40* (3), 337-357; (b) Tanaka, K.; Suzuki, N.; Nishida, G., Cationic Rhodium(I)/Modified-BINAP Catalyzed [2+2+2] Cycloaddition of Alkynes with Nitriles. *European Journal of Organic Chemistry* **2006,** (17), 3917-3922; (c) Shibata, T.; Uchiyama, T.; Endo, K.,

Enantioselective Synthesis of Chiral Tripodal Cage Compounds by [2+2+2] Cycloaddition of Branched Triynes. *Organic Letters* **2009,** *11* (17), 3906-3908.

5. Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P., The chemistry of titanacyclopentadiene rings supported by 2,6-diphenylphenoxide ligation: stoichiometric and catalytic reactivity. *Organometallics* **1993,** *12* (8), 2911-2924.

6. Strickler, J. R.; Bruck, M. A.; Wigley, D. E., Synthesis and characterization of a substituted .eta.2-pyridine complex of tantalum prepared by [2+2+2] cycloaddition chemistry. *Journal of the American Chemical Society* **1990,** *112* (7), 2814-2816.

7. (a) Takahashi, T.; Tsai, F.-Y.; Kotora, M., Selective Formation of Substituted Pyridines from Two Different Alkynes and a Nitrile: Novel Coupling Reaction of Azazirconacyclopentadienes with Alkynes. *Journal of the American Chemical Society* **2000,** *122* (20), 4994-4995; (b) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J., A Nickel-Catalyzed Route to Pyridines. *Journal of the American Chemical Society* **2005,** *127* (14), 5030-5031; (c) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J., An in Situ Approach for Nickel-Catalyzed Cycloaddition. *Journal of Organic Chemistry* **2006,** *71* (15), 5834-5836.

8. (a) Wang, C.; Li, X.; Wu, F.; Wan, B., A Simple and Highly Efficient Iron Catalyst for a [2+2+2] Cycloaddition to Form Pyridines. *Angewandte Chemie International Edition* **2011,** *50* (31), 7162-7166; (b) D'Souza, B. R.; Lane, T. K.; Louie, J., Iron-Catalyzed Cycloaddition of Alkynenitriles and Alkynes. *Organic Letters* **2011,** *13* (11), 2936-2939.

9. (a) Wakatsuki, Y.; Yamazaki, H., Novel synthesis of heterocyclic compounds from acetylenes. *Journal of the Chemical Society, Chemical Communications* **1973,** (8), 280-

280; (b) Wakatsuki, Y.; Yamazaki, H., Cobalt-catalyzed synthesis of pyridines from acetylenes and nitriles. *Tetrahedron Letters* **1973,** *14* (36), 3383-3384; (c) Vollhardt, K. P. C.; Bergman, R. G., One-step synthesis of benzocyclobutenes involving cooligomerization of linear mono- and diacetylenes catalyzed by 5-cyclopentadienylcobalt dicarbonyl. *Journal of the American Chemical Society* **1974,** *96* (15), 4996-4998; (d) Bönnemann, H.; Brinkmann, R.; Schenkluhn, H., Eine einfache, kobalt-katalysierte Pyridin-Synthese. *Synthesis* **1974,** *1974* (08), 575-577; (e) BÖNnemann, H.; Brinkmann, R., Eine kobalt-katalysierte Einstufen-Synthese von Dipyridinen. *Synthesis* **1975,** *1975* (09), 600-602; (f) Yamazaki, H.; Wakatsuki, Y., Cobalt metallocycles : I. One-step and stepwise synthesis of cobaltacyclopentadiene complexes from acetylenes. *Journal of Organometallic Chemistry* **1977,** *139* (2), 157-167; (g) Bönnemann, H., Organocobalt compounds in the synthesis of pyridines–an example of structure-effectivity relationships in homogeneous catalysis. *Angewandte Chemie International Edition in English* **1985,** *24* (4), 248-262; (h) Young, D. D.; Deiters, A., A General Approach to Chemo- and Regioselective Cyclotrimerization Reactions. *Angewandte Chemie International Edition* **2007,** *46* (27), 5187-5190.

10. (a) Vollhardt, K. P. C., Transition-metal-catalyzed acetylene cyclizations in organic synthesis. *Accounts of Chemical Research* **1977,** *10* (1), 1-8; (b) Vollhardt, K. P. C., Cobalt-Mediated [2 + 2 + 2]-Cycloadditions: A Maturing Synthetic Strategy [New Synthetic Methods]. *Angewandte Chemie International Edition in English* **1984,** *23* (8), 539-556; (c) Schore, N. E., Transition metal-mediated cycloaddition reactions of alkynes in organic synthesis. *Chemical Reviews* **1988,** *88* (7), 1081-1119; (d) Saito, S.;

Yamamoto, Y., Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives. *Chemical Reviews* **2000,** *100* (8), 2901-2916; (e) Varela, J. A.; Saá, C., Construction of Pyridine Rings by Metal-Mediated [2 + 2 + 2] Cycloaddition. *Chemical Reviews* **2003,** *103* (9), 3787-3802; (f) Gandon, V.; Aubert, C.; Malacria, M., Recent progress in cobalt-mediated [2 + 2 + 2] cycloaddition reactions. *Chemical Communications* **2006,** (21), 2209-2217; (g) Chopade, P. R.; Louie, J., [2+2+2] Cycloaddition Reactions Catalyzed by Transition Metal Complexes. *Advanced Synthesis & Catalysis* **2006,** *348* (16-17), 2307-2327; (h) Heller, B.; Hapke, M., The fascinating construction of pyridine ring systems by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions. *Chemical Society Reviews* **2007,** *36* (7), 1085-1094; (i) Varela, J. A.; Saá, C., Recent Advances in the Synthesis of Pyridines by Transition-Metal-Catalyzed [2+2+2] Cycloaddition. *Synlett* **2008,** 2571-2578; (j) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V., Air-Stable $\{(C_5H_5)Co\}$ Catalysts for [2+2+2] Cycloadditions. *Angewandte Chemie International Edition* **2009,** *48* (10), 1810-1813.

11. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P., Synthetic applications and mechanism studies of the decarbalkoxylations of geminal diesters and related systems effected in dimethyl sulfoxide by water and/or by water with added salts. *Journal of Organic Chemistry* **1978,** *43* (1), 138-147.

12. (a) Caine, D.; Procter, K.; Cassell, R. A., A facile synthesis of (-)-R-5-methyl-2-cyclohexen-1-one and related 2-substituted enones from (+)-pulegone. *The Journal of*

Organic Chemistry **1984,** *49* (14), 2647-2648; (b) Reusch, W.; Johnson, C. K., The Pulegone Oxides. *The Journal of Organic Chemistry* **1963,** *28* (10), 2557-2560; (c) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P., Enantiospecific synthesis of RPR 107880: A new non peptide substance P antagonist. *Tetrahedron Letters* **1996,** *37* (18), 3125-3128.

13. (a) Krause, N., Substituent effects and complexation phenomena in the diastereoselective protonation of chiral enolates. *Angewandte Chemie International Edition in English* **2003,** *33* (17), 1764-1765; (b) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H., Regio- and Stereocontrolled Synthesis of Allenic and Acetylenic Derivatives. Organotitanium and Boron Reagents. *Bulletin of the Chemical Society of Japan* **1984,** *57* (10), 2768-2776; (c) Krause, N.; Mackenstedt, M., Preparation of the first polymeric, chelating proton donors and their use in diastereoselective protonations of chiral enolates. *Tetrahedron Letters* **1998,** *39* (52), 9649-9650.

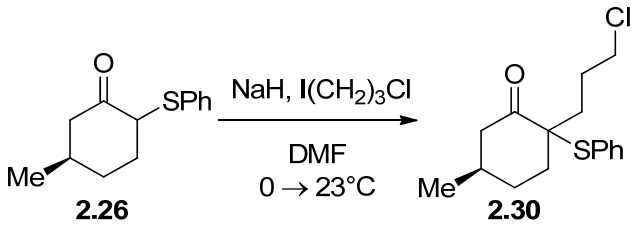
14. (a) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I., Copper (I)-Catalyzed Amination of Propargyl Esters. Selective Synthesis of Propargylamines, 1-Alken-3-ylamines, and (Z)-Allylamines. *Journal of Organic Chemistry* **1994,** *59* (9), 2282-2284; (b) Yokokawa, F.; Sugiyama, H.; Aoyama, T.; Shioiri, T., A General synthesis of N-reverse-prenyl indoles. *ChemInform* **2004,** *35* (42); (c) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M., A convenient method for the aromatic amino-Claisen rearrangement of N-(1, 1-disubstituted-allyl) anilines. *Synthesis* **2001,** (04), 621-625; (d) Francis, C. L.; Williamson, N. M.; Ward, A. D., The synthesis of tetrahydroquinolines related to virantmycin. *Synthesis* **2004,** (16), 2685-2691.

15. (a) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L., $Mg(ClO_4)_2$ as a Powerful Catalyst for the Acylation of Alcohols under Solvent-Free Conditions. *Synletter* **2003,** *2003* (01), 39-42; (b) Song, Y.; Okamoto, S.; Sato, F., A concise asymmetric synthesis of 5,8-disubstituted indolizidine alkaloids. Total synthesis of (−)-indolizidine 209B. *Tetrahedron Letters* **2002,** *43* (48), 8635-8637.

16. (a) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S., Total synthesis of lycopodium alkaloids: (±)-lycopodine, (±)-lycodine, and (±)-lycodoline. *Journal of the American Chemical Society* **1982,** *104* (4), 1054-1068; (b) Kleinman, E.; Heathcock, C. H., Total synthesis of (±)-Lycodine. *Tetrahedron Letters* **1979,** *20* (43), 4125-4128; (c) Tsukano, C.; Zhao, L.; Takemoto, Y.; Hirama, M., Concise Total Synthesis of (±)-Lycodine. *European Journal of Organic Chemistry* **2010,** *2010* (22), 4198-4200.

17. Gray, B. L.; Wang, X.; Brown, W. C.; Kuai, L.; Schreiber, S. L., Diversity Synthesis of Complex Pyridines Yields a Probe of a Neurotrophic Signaling Pathway. *Organic Letters* **2008,** *10* (13), 2621-2624.

2.7 Experimental Section



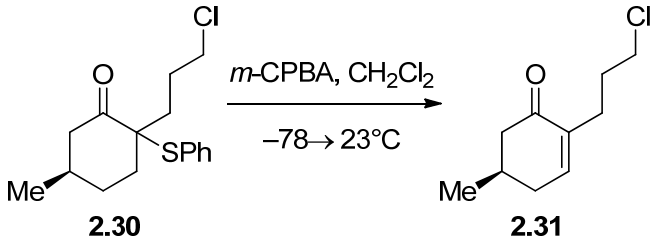
2.26 **2.30**

To a solution of thioether **2.26** (5.0 g, 22.7 mmol, 1.0 equiv.) in DMF (120 mL) at 0 °C solid NaH (1.04 g, 60% oil dispersion, 26.0 mmol, 1.2 equiv.) was added in portions over five minutes with extensive gas evolution. After 60 min the 1-chloro-3-iodopropane (5.10 g, 25.0 mmol, 1.1 equiv.) was added dropwise over 10 minutes and the cooling bath was removed and the solution was stirred for 1 hour. The reaction mixture was diluted with aqueous saturated NH_4Cl solution (500 mL) and EtOAc (250 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 2/1 hexanes/Et_2O) to afford yellow paste **2.30** (3.54 g, 53%).

2.30: $\mathbf{R}_f$ = 0.45 (silica gel, Hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$, **2.30-major**: **2.30-minor** = 0.77 : 0.23 Mixture of Diastereomers): δ 0.96 (d, J = 6.4 Hz, 3H**), 1.08 (d, J = 6.4 Hz, 3H*), 1.42-1.72 (m, 3H), 1.72-2.02 (m, 4H), 2.04-2.15 (m, 2H), 2.28-2.34 (m, 1H), 3.12 (t, J = 13.2 Hz, 1H*), 3.30 (dd, J = 5.2 and 14.0 Hz, 1H**), 3.44-3.54 (m, 2H), 7.27-7.50 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.6, 21.9, 22.2, 27.0, 27.1, 27.8, 29.6, 31.86, 31.91, 32.2, 33.5, 34.5, 35.7, 45.0, 45.1, 45.8, 59.7, 61.4, 128.86, 128.95, 129.0, 129.3, 129.5, 135.3, 136.0, 136.5, 207.2, 207.9; **IR**: ν 2955, 2927, 1701, 1438 cm^{-1}; **HRMS** calcd. for $C_{16}H_{21}ClOS^+$ [M^+]: 296.1002. Found: 296.1005.

H* for minor isomer

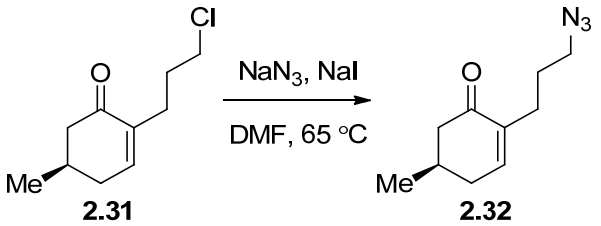
H**for major isomer



2.30 **2.31**

To a solution of ketone **2.30 (**3.67 g, 12.4 mmol, 1.0 equiv.**)** in CH_2Cl_2 (150 mL) at –78 °C a solution of purified *m*CPBA (2.24 g, 13.0 mmol, 1.1 equiv.) in CH_2Cl_2 (50 mL) was added over 1 hour. The mixture was warmed to 23 °C over one hour then stirred 10 hours where upon the solution became homogeneous. The reaction was diluted with aqueous $NaHSO_3$ solution (10% w/w, 50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 → 2/1 hexanes/Et_2O) to afford **2.31** as yellow oil (1.9 g, 82%).

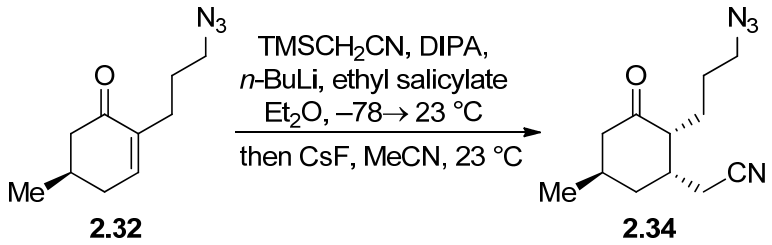
2.31: $\mathbf{R}_f$ = 0.50 (silica gel, hexanes/ EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.03 (d, J = 6.0 Hz, 3H), 1.82-1.89 (m, 2H), 1.99-2.09 (m, 2H), 2.12-2.21 (m, 1H), 2.31 (t, J = 7.6 Hz, 2H), 2.37-2.50 (m, 2H), 3.48 (t, J = 6.4 Hz, 2H), 6.72-6.74 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 26.9, 30.6, 31.2, 34.3, 44.5, 46.5, 137.8, 145.5, 199.4; **IR** (neat): ν 2957, 1675, 1384 cm^{-1}; **HRMS** calcd. for $C_{10}H_{16}ClO^+$ [M+H$^+$]: 187.0890. Found: 187.0890.



2.31 **2.32**

To a solution of enone **2.31 (**231 mg, 1.24 mmol, 1.0 equiv.**)** in DMF (10 mL) at 23 °C solid NaI (403 mg, 2.7 mmol, 2.2 equiv.) and NaN_3 (159 mg, 2.5 mmol, 2.0 equiv.) were added. The reaction flask was immersed into 65 °C oil bath and stirred for 24 hours. The reaction was diluted with aqueous saturated NH_4Cl solution (20 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 → 2/1 hexanes/EtOAc) to afford **2.32** as pale yellow oil (171 mg, 72%).

2.32: R_f = 0.50 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (d, J = 6.0 Hz, 3H), 1.66-2.00 (m, 2H), 2.01-2.27 (m, 5H), 2.38-2.45 (m, 1H), 2.45-2.51 (m, 1H), 3.25 (t, J = 6.8 Hz, 2H), 6.70-6.73 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 26.9, 27.8, 30.6, 34.3, 46.6, 51.0, 138.2, 145.3, 199.5; **IR** (neat): ν 2956, 2097, 1674 cm^{-1}; **HRMS** calcd. for $C_{10}H_{16}N_3O^+$ [M+H$^+$]: 194.1293. Found: 194.1291.

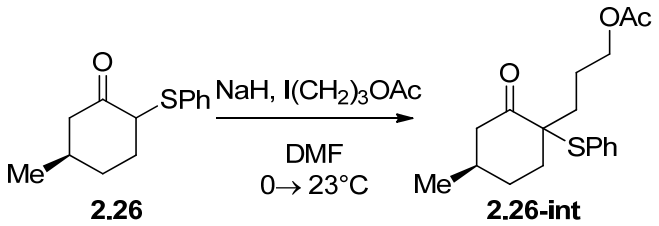


2.32 **2.34**

To s solution of the diisopropylamine (95 µL, 0.67 mmol, 2.0 equiv) in Et_2O (2 mL) *n*-BuLi solution (0.35 mL, 2.0 M, 0.67 mmol, 2.0 equiv) was added at –78 °C. After 5 minutes neat trimethylsilylacetonitrile (92 µL, 0.67 mmol, 2.0 equiv.) was added. After 30 min the solution was transferred via cannula to a second flask containing enone **2.32** (65 mg, 0.34 mmol, 1.0 equiv.) in Et_2O (5 mL) cooled to – 78 °C. After 25 minutes the resulting yellow solution was transferred via cannula to a third flask containing ethyl salicylate (0.15 mL, 1.0 mmol, 3.0 equiv.) in Et_2O (2 mL) cooled to – 78 °C. The reaction was allowed to slowly warm to 23 °C over 1 hour. The lithium phenoxide was quenched by the addition of acetic acid (60 µL, 1.0 mmol, 3 equiv.). The reaction was filtered through a pad of celite. The solution was washed with aqueous saturated $NaHCO_3$ solution (10 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel chromatography (20/1 → 1/1 hexanes/Et_2O) to afford yellow oil (42 mg, 72%) as a mixture of 4 diastereomers that was used in the next reaction (below).

To a solution of the above diastereomers (42 mg, 0.14 mmol, 1.0 equiv.) in MeCN (3 mL) solid CsF (5.0 mg, 0.030 mmol, 0.24 equiv.) was added. The resulting mixture was stirred at 23 °C for 6 hours then diluted with aqueous saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel chromatography (10/1 → 1/1 hexanes/EtOAc) to afford ketone **2.34** (27.8 mg, 87%) as a light yellow oil.

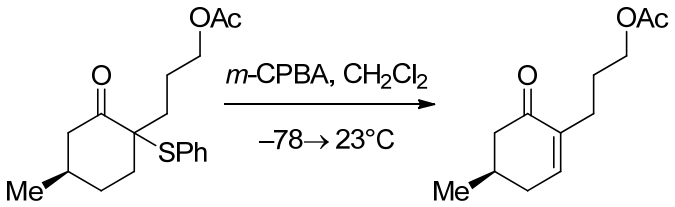
2.34: $\mathbf{R}_f$ = 0.65 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.08 (d, J = 6.4 Hz, 3H), 1.16-1.25 (m, 1H), 1.40-1.51 (m, 1H), 1.56-1.62 (m, 2H), 1.63-1.84 (m, 2H), 1.96-2.17 (m, 3H), 2.31-2.44 (m, 2H), 2.56-2.61 (m, 2H), 3.24-3.35 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9, 22.0, 23.7, 27.0, 30.0, 37.3, 38.3, 50.1, 51.3, 52.2, 118.2, 210.0; **IR**: ν 2954, 2098, 1709 cm^{-1}; **HRMS** calcd. for $C_{12}H_{18}N_4ONa^+$ [M + Na^+]: 257.1378. Found: 257.1373.



2.26 **2.26-int**

To a solution of thioether **2.26** (30.0 g, 136 mmol, 1.0 equiv.) in DMF (1.25 L) at 0 °C solid NaH (5.99 g, 60% oil dispersion, 150 mmol, 1.1 equiv.) was added portion wise over five minutes with extensive gas evolution. After 60 minutes the iodo ester (37.3 g, 163 mmol, 1.2 equiv.) was added neat, dropwise over 10 minutes then the cooling bath was removed and the resulting solution was stirred at 23 ºC for 1 hour. The reaction was diluted with aqueous saturated NH_4Cl solution (2 L) and EtOAc (1 L). The organic phase was collected and the aqueous phase was extracted with EtOAc (4 × 500 mL). The combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 2/1 hexanes/Et_2O) to afford a diastereomeric mixture of ketones **2.26-int** as yellow viscous oil (27.3 g, 63%).

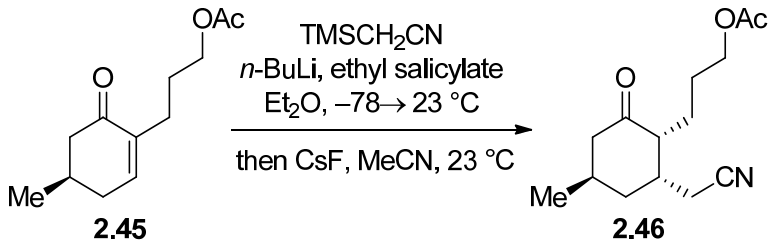
2.26-int: R_f = 0.31 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$, 7/3 Mixture of Diastereomers): δ 0.88 (t, J = 6.8 Hz, 0.7 H), 0.96 (d, J = 6.8 Hz, 2.1 H), 1.08 (d, J = 6.0 Hz, 0.9 H), 1.22-1.30 (m, 0.3 H), 1.46-1.94 (m, 5 H), 1.96-2.36 (m, 7 H), 3.14 (t, J = 13.2 Hz, 0.3 H), 3.35 (dd, J = 6.0 and 14.4 Hz, 0.7 H), 3.98-4.04 (m, 2H), 7.26-7.37 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.3, 20.7, 22.0, 22.5, 22.7, 27.5, 29.5, 30.2, 30.6, 31.6, 33.0, 34.3, 35.4, 44.7, 45.6, 59.6, 60.8, 61.2, 64.2, 64.3, 128.6, 128.7, 129.1, 129.2, 129.9, 130.1, 135.8, 136.3, 170.8, 206.9, 207.7; **IR**: ν 1739, 1700, 1043 cm^{-1}; **HRMS** calcd. for $C_{18}H_{24}O_3SNa^+$ [M+Na^+]: 343.13438. Found: 343.13447.



2.26-int **2.45**

The diastereomeric mixture of ketones **2.26-int (**27.0 g, 84 mmol, 1.0 equiv.**)** in CH_2Cl_2 (1.0 L) was cooled to –78 °C and a solution of purified *m*-CPBA (15.3 g, 88 mmol, 1.05 equiv.) in CH_2Cl_2 (600 mL) was added over 1 hour. The cooling bath was removed and the solution was stirred for 10 hours at 23 ºC where upon the solution became homogeneous. The reaction was then diluted with aqueous $NaHSO_3$ (10% w/w, 200 mL). The mixture was extracted with EtOAc (3 × 400 mL). The organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (10/1 → 2/1 hexanes/Et_2O) to afford enone **2.45** as yellow oil (13.6 g, 77%).

2.45: $\mathbf{R}_f$ = 0.39 (silica gel, Hexanes/EtOAc = 5/1); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.05 (d, J = 6.4 Hz, 3H), 1.58-1.77 (m, 2H), 2.04-2.09 (m, 4H), 2.09-2.13 (m, 1H), 2.13-2.19 (m, 1H), 2.25 (t, J = 8.0 Hz, 2H), 2.41 (dt, J = 5.0 and 18.0 Hz, 1H), 2.47-2.52 (m, 1H), 4.04 (t, J = 6.4 Hz, 2H), 6.68-6.70 (m, 1H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.0, 21.2, 26.0, 27.3, 30.6, 34.3, 46.6, 64.0, 138.3, 144.9, 171.2, 199.5; **IR** (neat): ν 1734, 1717 cm^{-1}; **HRMS** calcd. for $C_{12}H_{18}O_3Na^+$ [M+Na^+]: 233.11536. Found: 233.11490.

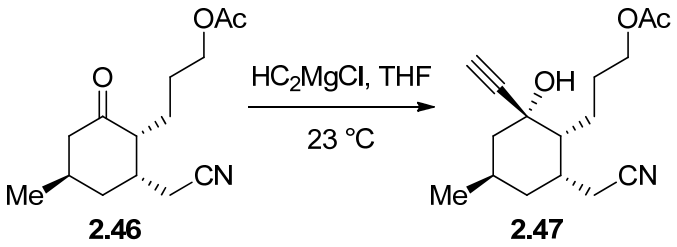


2.45 **2.46**

To a solution of trimethylsilyl acetonitrile (0.28 mL, 2.1 mmol, 1.3 equiv.) in Et_2O (30 mL) at −78 °C was added a solution of *n*-butyllithium (1.8 M Hexanes, 1.1 mL, 2.0 mmol, 1.2 equiv.) over one minute. After stirring for 40 minutes at −78 °C the pale yellow solution was transferred over 3 minutes via cannula to a stirred solution of the enone **2.45** (350 mg, 1.7 mmol, 1.0 equiv.) in Et_2O (30 mL) at −78 °C. After 30 minutes, the bright yellow solution was added over 3 minutes via cannula to a stirred solution of ethyl salicylate (0.97 mL, 6.6 mmol, 4.0 equiv.) at −78 °C in Et_2O (30 mL). After 5 minutes the cooling bath was removed and the reaction was allowed to warm to 23 ºC over 20 minutes and acetic acid (0.10 mL, 1.7 mmol, 1.1 equiv.) was added in one portion. The solution was washed with aqueous saturated sodium bicarbonate solution (50 mL). The organic extract was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford a mixture of diastereomers as light yellow oil (300 mg, 56%)

To a solution of the above diastereomers (4.50 g, 13.9 mmol, 1.0 equiv.) in MeCN (110 mL) at 23 °C was added solid CsF (0.20 g, 1.3 mmol, 0.10 equiv.). The resulting mixture was stirred at 23 ºC for six hours. The reaction was diluted with aqueous saturated NH_4Cl solution (100 mL) and extracted with EtOAc (2 × 200 mL). The organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 → 1/1 hexanes/Et_2O) to afford ketone **2.46** (2.80 g, 80%) as yellow oil. The two steps yield is 45%.

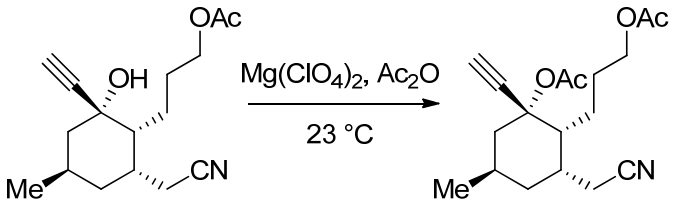
2.46: $\mathbf{R}_f$ = 0.45 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.0 Hz, 3H), 1.15-1.23 (m, 1H), 1.48-1.84 (m, 4H), 1.95-2.17 (m, 7H), 2.31-2.44 (m, 2H), 2.56-2.63 (m, 2H), 3.99-4.09 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.8, 20.9, 22.0, 22.8, 26.5, 30.0, 37.2, 38.1, 50.1, 52.0, 64.0, 118.2, 171.1, 210.1; **IR**: 1735, 1710, 1048 cm^{-1}; **HRMS** calcd. for $C_{14}H_{21}NO_3Na^+$ [M+Na$^+$]: 274.14191. Found: 274.14169.



2.46 **2.47**

To a solution of ketone **2.46** (11.5 g, 45.8 mmol, 1.0 equiv.) in THF (350 mL) at 23 °C a solution of the ethynyl magnesium chloride (114 mL, 0.60 M in toluene/THF, 69 mmol, 1.5 equiv.) was added dropwise over five minutes. After 30 minutes the resulting alkoxide was quenched by the addition of aqueous saturated NH_4Cl solution (100 mL) and the mixture was extracted with EtOAc (3 × 200 mL). The organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude alcohol was purified by silica gel chromatography (5/1 → 2/1 hexanes/EtOAc) to afford alcohol **2.47** (12.3 g, 97%) as a yellow oil.

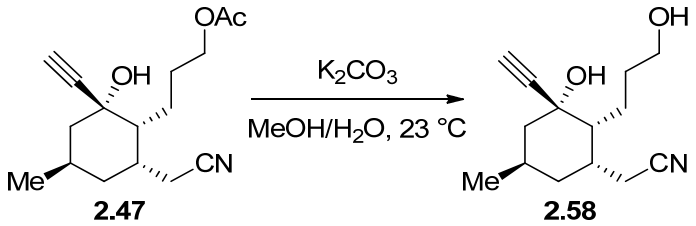
2.47: $\mathbf{R}_f$ = 0.41 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.8 Hz, 3H), 1.18-1.25 (m, 1H), 1.41-1.66 (m, 3H), 1.70-1.79 (m, 2H), 1.83-1.93 (m, 1H), 1.93-2.04 (m, 2H). 2.06 (s, 3H), 2.20-2.26 (m, 1H), 2.45-2.51 (m, 2H), 2.80 (dd, J = 8.8 and 17.6 Hz, 1H), 2.92 (dd, J = 0.4 and 14.8 Hz, 1H), 4.04-4.16 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9, 21.0, 21.4, 21.5, 23.2, 25.9, 32.2, 37.6, 45.5, 49.3, 64.2, 70.9, 72.2, 87.5, 120.4, 171.1; **IR**: ν 3462, 1738, 1457, 1024 cm^{-1}; **HRMS** calcd. for $C_{16}H_{23}NO_3Na^+$ [M+Na$^+$]: 300.15756. Found: 300.15724.



2.47 **2.48**

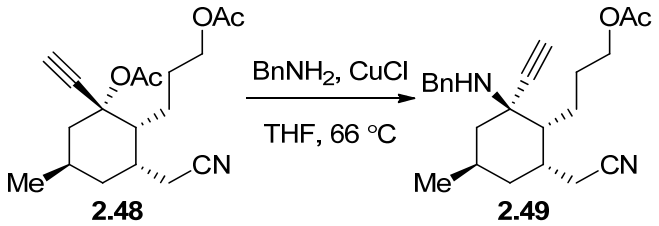
To a solution of alcohol **2.47** (9.0 g, 32 mmol, 1.0 equiv.) in acetic anhydride (27.6 mL, 92 mmol, 2.8 equiv.) at 23 °C solid magnesium perchlorate (0.70 g, 3.1 mmol, 0.1 equiv.) was added in one portion. After 30 minutes the mixture was diluted with aqueous saturated $NaHCO_3$ solution (200 mL) and solid $NaHCO_3$ was added to adjust the pH to 8. The mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude acetate was purified by silica gel chromatography (5/1 → 2/1 hexanes/EtOAc) to yield diacetate **2.48** (10.1 g, 97%) as a yellow oil.

2.48: $\mathbf{R}_f$ = 0.45 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (d, J = 6.4 Hz, 3H), 1.24-1.33 (m, 2H), 1.44-1.64 (m, 4H), 1.69-1.78 (m, 2H), 2.04 (s, 3H), 2.06 (s, 3H), 2.08-2.14 (m, 2H), 2.31-2.34 (m, 1H), 2.52-2.54 (m, 1H), 2.59 (s, 1H), 2.97 (td, J = 2.8 and 14.8 Hz, 1H), 4.05-4.16 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.0, 21.0, 21.3, 21.6, 22.0, 23.0, 25.9, 32.1, 37.3, 43.1, 46.8, 64.0, 74.5, 77.5, 82.7, 119.8, 168.2, 171.1; **IR**: ν 1737, 1727 cm^{-1}; **HRMS** calcd. for $C_{18}H_{25}NO_4Na^+$ [M+Na^+]: 342.16813. Found: 342.16774.



To a solution of acetate **2.47** (100 mg, 0.36 mmol, 1.0 equiv.) in methanol (5 mL) and water (0.1 mL) solid potassium carbonate (248 mg, 1.80 mmol, 5.0 equiv.) was added. The mixture was stirred for 12 hours then diluted with aqueous saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to provide **2.58** as colorless crystals (59.9 mg, 71%, m.p. 89.0 - 92.1 °C).

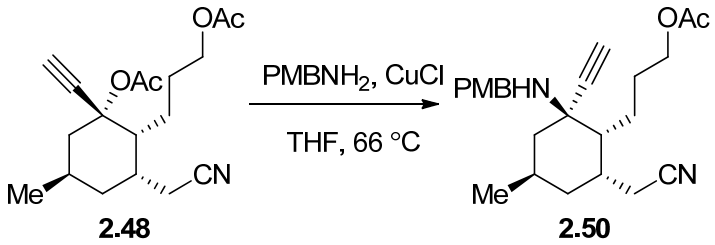
2.58: $\mathbf{R}_f$ = 0.15 (silica gel, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.4 Hz, 3H), 1.20-1.26 (m, 1H), 1.41-1.48 (m, 1H), 1.51-1.73 (m, 7H), 1.82-1.92 (m, 1H), 2.02-2.08 (m, 2H), 2.22-2.24 (m, 1H), 2.48 (s, 1H), 2.50-2.55 (m, 1H), 2.77 (dd, J = 11.6 and 17.6 Hz, 1H), 3.64-3.75 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9, 21.4, 21.5, 23.1, 29.9, 32.2, 37.8, 45.7, 49.3, 62.8, 71.1, 72.2, 87.6, 120.6; **IR**: ν 3299, 2918, 2248 cm^{-1}; **HRMS** calcd. for $C_{14}H_{22}NO_2^+$ [M +H$^+$]: 236.1651. Found: 236.1645.



2.48 **2.49**

A flask containing neat benzyl amine (1.2 mL, 11 mmol, 3.5 equiv.) and diacetate **2.48** (1.0 g, 3.1 mmol, 1 equiv.) was evacuated and backfilled with N_2 three times. By syringe THF (24 mL) was added and the mixture was degassed via iterative freeze-pump-thaw sequences (3 cycles). Solid CuCl (105 mg, 1.1 mmol, 0.34 equiv.) was added in one portion with a back flow of N_2. The reaction flask was placed in an 80 °C oil bath for 30 minutes, then cooled to 23 °C, and diluted with pentane (100 mL). The mixture was filtered through silica gel (EtOAc/hexanes = 1/1) and concentrated to provide amine **2.49** (1.05 g, 92%) as yellow oil.

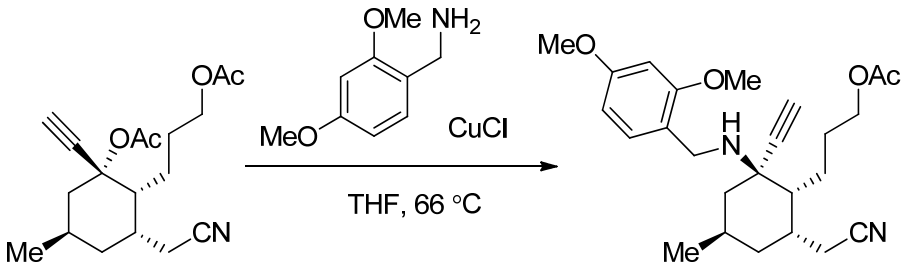
2.49: $\mathbf{R}_f$ = 0.35 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01(d, J = 6.4 Hz, 3H), 1.10 (t, J = 12.0 Hz, 1H), 1.20-1.27 (m, 1H), 1.43-1.65 (m, 4H), 1.72-1.91 (m, 2H), 2.01 (s, 3H), 2.02-2.06 (m, 1H), 2.22 (m, 1H), 2.30-2.35 (m, 1H), 2.46 (s, 1H), 2.56 (dd, J = 2.4 and 17.2 Hz, 1H), 3.00 (dd, J = 12.4 and 17.2 Hz, 1H), 3.80 (dd, J = 12.0 and 49.6 Hz, 2H), 4.04-4.07 (m, 2H), 7.25-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5, 20.8, 21.8, 22.7, 23.8, 25.9, 33.0, 37.7, 46.2, 46.4, 47.0, 55.7, 64.0, 74.7, 86.6, 120.0, 127.0, 128.3, 128.4, 140.3, 171.0; **IR**: ν 2953, 1737 cm^{-1}; **HRMS** calcd. for $C_{23}H_{31}N_2O_2^+$ [M+H$^+$]: 367.23855. Found: 367.23794.



2.48 **2.50**

A flask containing *p*-methoxylbenzylamine (2.0 mL, 15.3 mmol, 4.1 equiv.) and acetate **2.48** (1.20 g, 3.8 mmol, 1.0 equiv.) was evacuated and backfilled with N_2 three times. By syringe THF (28 mL) was added and the mixture was degassed via iterative freeze-pump-thaw sequences (3 cycles). To the degassed solution solid CuCl (110 mg, 1.08 mmol, 0.29 equiv.) was added in one portion with a back flow of N_2. The flask was immersed into an 80 °C oil bath for 30 minutes, cooled to 23 °C, and diluted with pentane (100 mL). The mixture was filtered through silica gel (hexanes/EtOAc = 1/1) and concentrated to provide **2.50** (1.20 g, 81%) as pale yellow oil.

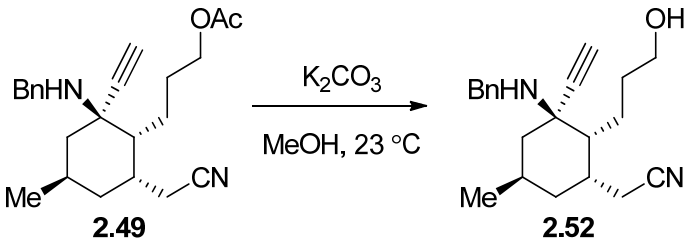
2.50: $\mathbf{[\alpha]^{24}_D}$ -38.2° (*c* 0.19, CH_2Cl_2); $\mathbf{R}_f$ = 0.30 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (d, J = 6.4 Hz, 3H), 1.09 (t, J = 12.4 Hz, 1H), 1.19-1.27 (m, 2H), 1.44-1.64 (m, 3H), 1.72-1.77 (m, 2H), 1.83-1.89 (m, 1H), 2.01-2.06 (m, 4H), 2.17-2.23 (m, 1H), 2.31-2.35 (m, 1H), 2.46 (s, 1H), 2.53-2.58 (m, 1H), 3.0 (dd, J = 9.0 and 16.8 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.78-3.81 (m, 4H), 4.03-4.07 (m, 2H), 6.84-6.88 (m, 2H), 7.23-7.25 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5, 20.9, 21.9, 22.8, 23.8, 26.0, 33.0, 37.7, 46.2, 46.5, 46.5, 55.3, 55.7, 64.1, 74.7, 86.8, 113.9, 120.1, 129.6, 132.4, 158.8, 171.1; **IR**: ν 3287, 1735 cm^{-1}; **HRMS** calcd. for $C_{24}H_{33}N_2O_3^+$ [M+H$^+$]: 397.24912. Found: 397.24867.



2.48 **2.51**

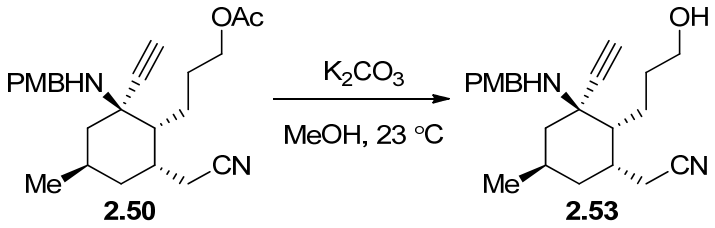
A flask containing 3,4-dimethoxylbenzylamine (0.22 mL, 1.5 mmol, 2.5 equiv.) and diacetate **2.48** (185 mg, 0.58 mmol, 1.0 equiv.) was evacuated and backfilled with N_2 three times. By syringe THF (6 mL) was added and the mixture was degassed via iterative freeze-pump-thaw sequences (three times). Solid CuCl (25 mg, 0.25 mmol, 0.44 equiv.) was added in one portion with a back flow of N_2. The reaction flask was placed in an 80 °C oil bath for 20 minutes, cooled to 23 °C, and diluted with pentane (50 mL). The mixture was filtered through silica gel (hexanes/EtOAc = 1/1) and concentrated to provide amine **2.51** (190 mg, 77%) as pale yellow oil.

2.51: $\mathbf{R}_f$ = 0.30 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 3H), 1.11 (t, J = 12.4 Hz, 1H), 1.18-1.25 (m, 1H), 1.43-1.67 (m, 3H), 1.68-1.79 (m, 4H), 1.83-1.93 (m, 1H), 2.01-2.07 (m, 4H), 2.22 (dt, J = 2.8 and 12.8 Hz, 1H), 2.30-2.33 (m, 1H), 2.44 (s, 1H), 2.57 (dd, J = 2.8 and 17.2 Hz, 1H), 3.01 (dd, J = 12.0 and 17.2 Hz, 1H), 3.61 (d , J = 12.0 Hz, 1H), 3.79 (s, 3H), 3.81-3.84 (m, 4H), 4.05-4.08 (m, 2H), 6.42-6.47 (m, 2H), 7.14-7.17 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5, 20.9, 21.9, 22.7, 23.8, 25.9, 33.1, 37.8, 42.0, 46.0, 46.2, 55.3, 55.4, 55.5, 64.3, 74.7, 86.7, 98.6, 104.1, 120.2, 120.7, 130.4, 158.5, 160.1, 171.1; **IR**: ν 3279, 2953, 2919, 1735 cm^{-1}; **HRMS** calcd. for $C_{25}H_{35}N_2O_4^+$ [M +H$^+$]: 427.25968. Found: 427.25929.



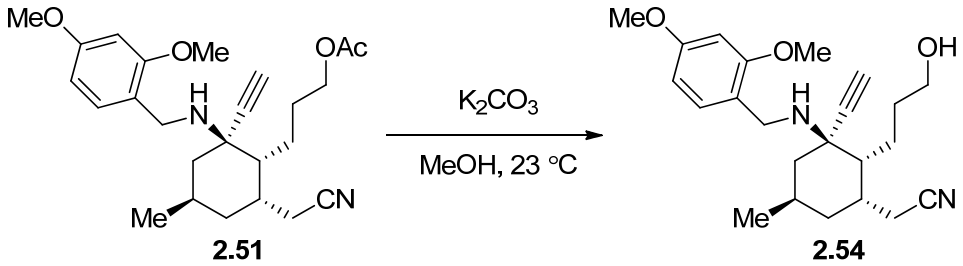
To a solution of the propargylamine **2.49** (1.70 g, 4.64 mmol, 1.0 equiv.) in methanol (25 mL) was added solid K_2CO_3 (3.0 g, 21.7 mmol, 4.7 equiv) in one portion. The heterogeneous solution was stirred vigorously for seven hours at 23 °C and then diluted with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 50 mL). The organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to provide alcohol **2.52** (1.50 g, 99%) as yellow oil.

2.52: $[\alpha]^{24}_{D}$ -73.9° (*c* 0.70, CH_2Cl_2); R_f = 0.30 (silica gel, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (d, J = 6.4 Hz, 3H), 1.10 (t, J = 12.0 Hz, 1H), 1.20-1.27 (m, 1H), 1.41-1.89 (m, 8H), 2.00-2.06 (m, 1H), 2.19-2.25 (m, 1H), 2.31-2.38 (m, 1H), 2.46 (s, 1H), 2.59-2.64 (m, 1H), 2.98 (dd, J = 12.0 and 17.2 Hz, 1H), 3.63-3.68 (m, 2H), 3.73 (d, J = 11.6 Hz, 1H), 3.84 (d, J = 11.6 Hz, 1H), 7.25-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5, 21.9, 22.6, 23.8, 29.7, 33.1, 37.8, 46.1, 46.5, 47.2, 55.9, 62.4, 74.8, 86.7, 120.3, 127.1, 128.48, 128.52, 140.2; **IR**: ν 3344, 3063, 2924, 2867, 1454, 733 cm^{-1}; **HRMS** calcd. for $C_{42}H_{56}N_4O_2^{2+}$ [2M $^{2+}$]: 324.22016. Found: 324.21988.



To a solution of the propargylamine **2.50** (1.20 g, 3.0 mmol, 1.0 equiv.) in methanol (20 mL) was added solid K_2CO_3 (2.0 g, 14.5 mmol, 4.8 equiv) in one portion. The heterogeneous solution was stirred vigorously for 7 hours at 23 °C, then diluted with saturated aqueous NH_4Cl solution (60 mL), and extracted with EtOAc (3 × 50 mL). The organic extracts were washed with aqueous saturated sodium chloride solution (20 mL), dried over Na_2SO_4, filtered, and concentrated to provide the corresponding alcohol **2.53** (1.07 g, 99%) as yellow oil.

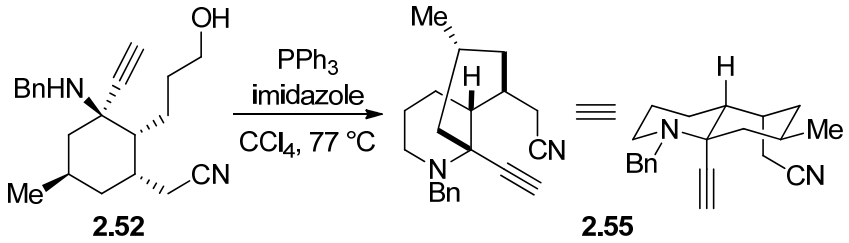
2.53: $[\alpha]^{24}_{D}$ -51.8° (*c* 0.55, CH_2Cl_2); R_f = 0.21 (silica gel, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (d, *J* = 6.4 Hz, 3H), 1.09 (t, *J* = 12.0 Hz, 1H), 1.21- 1.27 (m, 2H), 1.41-1.50 (m, 3H), 1.62-1.75 (m, 3H), 1.81-1.90 (m, 1H), 2.01-2.04 (m, 1H), 2.18-2.22 (m, 1H), 2.31-2.34 (m, 1H), 2.47 (s, 1H), 2.61 (dd, *J* = 3.6 and 17.2 Hz, 1H), 2.97 (dd, *J* = 12.0 and 17.2 Hz, 1H), 3.58-3.67 (m, 3H), 3.78-3.81 (m, 4H), 6.84-6.90 (m, 2H), 7.23-7.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5, 21.9, 22.6, 23.8, 29.7, 33.0, 37.8, 46.1, 46.4, 46.6, 55.3, 55.8, 62.4, 74.7, 86.8, 113.9, 120.3, 129.6, 132.3, 158.7; **IR**: *v* 3406, 1510, 1243, 1033 cm^{-1}; **HRMS** calcd. for $C_{22}H_{31}N_{22}O_2^+$ $[M+H^+]$: 355.23855. Found: 355.23805.



2.51 **2.54**

To a solution of **2.51** (195 mg, 0.46 mmol, 1.0 equiv.) in methanol (5.0 mL) and water (0.10 mL) was added solid K_2CO_3 (300 mg, 2.2 mmol, 4.8 equiv). The heterogeneous solution was stirred vigorously for 17 hours at 23 °C, then diluted with aqueous saturated NH_4Cl solution (40 mL), and extracted with EtOAc (3 × 40 mL). The organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to provide the corresponding alcohol **2.54** (166 mg, 94%) as yellow oil.

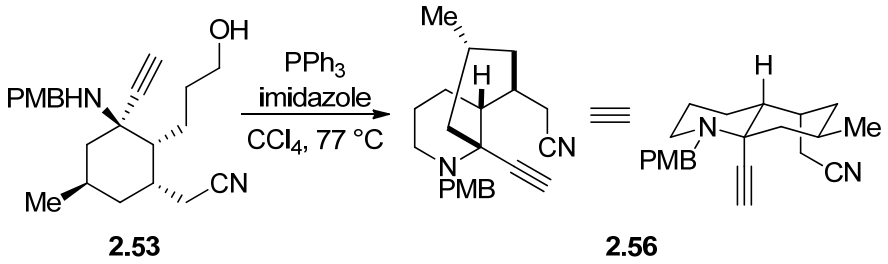
2.54: $\mathbf{R}_f$ = 0.30 (silica gel, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 3H),1.10 (t, J = 12.4 Hz, 1H), 1.20-1.24 (m, 1H), 1.39-1.55 (m, 2H), 1.63-1.72 (m, 2H), 1.77-2.04 (m, 5H), 2.23 (dt, J = 2.4 and 12.4 Hz, 1H), 2.30-2.34 (m, 1H), 2.44 (s, 1H), 2.62 (dd, J =2.8 ad 17.2 Hz, 1H), 2.99 (dd, J =12.0 and 17.2 Hz, 1H) 3.60-3.67 (m, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.84 (d, J = 11.6 Hz, 1H), 6.42-6.45 (m, 2H), 7.15 (dd, J = 2.0 and 6.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.6, 21.9, 22.6, 23.8, 29.8, 33.2, 37.9, 42.1, 45.9, 46.2, 55.3, 55.4, 55.7, 62.4, 74.7, 86.7, 98.7, 104.1, 120.4, 120.5, 130.5, 158.5, 160.2; **IR**: ν 3285, 2921, 1614 cm^{-1}; **HRMS** calcd. for $C_{23}H_{33}N_2O_3^+$ [M +H$^+$]: 385.24912. Found: 385.24852.



2.52 **2.55**

Alcohol **2.52** (750 mg, 2.3 mmol, 1.0 equiv.) was dissolved in CCl_4 (20 mL) and PPh_3 (1.21 g, 4.6 mmol, 2.0 equiv.) and imidazole (315 mg, 4.6 mmol, 2.0 equiv.) were added sequentially as solids. The reaction was placed in a heated oil bath for 15 hours then the oil bath was removed and the solution was diluted with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 25 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford alkyne-nitrile **2.55** (530 mg, 75%, m.p. 138.2-138.5 °C) as pale yellow crystalline solid.

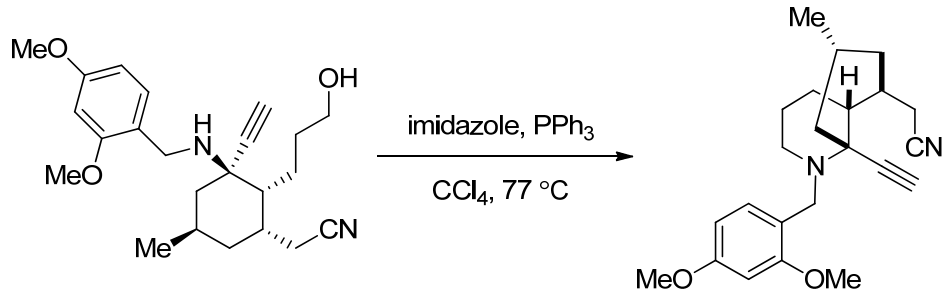
2.55: $[\alpha]^{24}_{D}$ –152.7° (*c* 1.0, CH_2Cl_2); R_f = 0.60 (silica gel, hexenes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (d, J = 6.4 Hz, 3H), 1.12 (t, J = 12.4 Hz, 1H), 1.25-1.66 (m, 6H), 1.93-2.01 (m, 2H), 2.11-2.15 (m, 1H), 2.26-2.34 (m, 2H), 2.51 (s, 1H), 2.55-2.63 (m, 2H), 2.93 (d, J = 13.6 Hz, 1H), 3.00 (dd, J = 12.0 and 18.0 Hz, 1H), 4.06 (d, J = 13.6 Hz, 1H), 7.20-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3, 22.2, 24.3, 25.9, 26.7, 37.2, 38.1, 45.9, 46.4, 48.5, 53.4, 58.6, 76.6, 83.6, 120.6, 126.6, 128.1, 128.5, 140.3; **IR**: ν 1454, 1068, 701 cm^{-1}; **HRMS** calcd. for $C_{21}H_{27}N_2^+$ [M+H$^+$]: 307.21742. Found: 307.21690.



2.53 **2.56**

The alcohol **2.53** (450 mg, 1.3 mmol, 1.0 equiv.) was dissolved in CCl_4 (15 mL) and PPh_3 (0.67 g, 2.54 mmol, 2.0 equiv.) and imidazole (172 mg, 2.5 mmol, 2.0 equiv.) were added sequentially as solids to the solution. The flask was placed in a heated oil bath for 15 hours, the oil bath was removed, and the solution was diluted with aqueous saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 5/1 hexanes/EtOAc) to afford **2.56** (530 mg, 74%) as pale yellow oil.

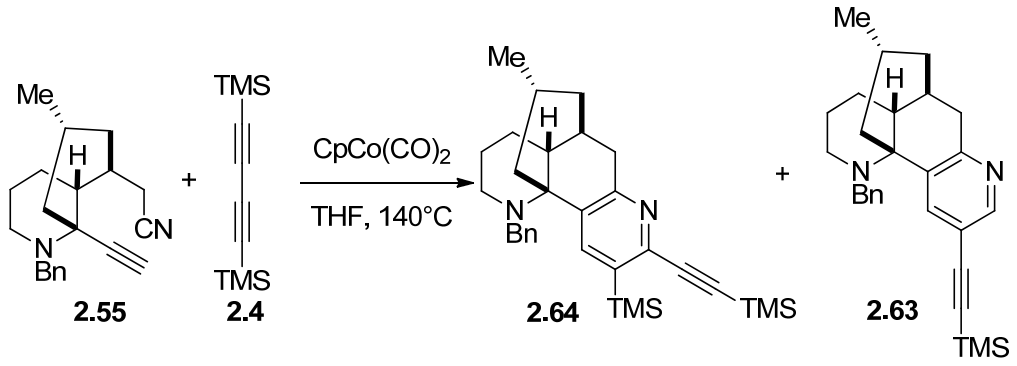
2.56: $[\alpha]^{24}_{D}$ –70.2° (*c* 0.69, CH_2Cl_2); R_f = 0.55 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.12 (t, *J* = 12.0 Hz, 1H), 1.28-1.75 (m, 6H), 1.93-2.00 (m, 2H), 2.11-2.15 (m, 1H), 2.22-2.29 (m, 2H), 2.50 (s, 1H), 2.54-2.63 (m, 2H), 2.86 (d, *J* = 13.2 Hz, 1H), 3.00 (dd, *J* = 12.0 and 21.2 Hz, 1H), 3.79 (s, 3H), 3.99 (d, *J* = 13.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.1, 22.1, 24.2, 25.7, 26.6, 37.1, 40.0, 45.8, 46.2, 48.1, 52.6, 55.1, 58.5, 76.6, 83.5, 113.4, 120.4, 129.4, 132.1, 158.3; **IR**: *v* 1512, 1243, 830 cm^{-1}; **HRMS** calcd. for $C_{22}H_{29}N_2O^+$ $[M+H]^+$: 337.22799. Found: 337.22731.



2.54 **2.57**

The alcohol **2.54** (250 mg, 0.65 mmol, 1.0 equiv.) was dissolved in CCl_4 (6 mL) then PPh_3 (0.34 g, 1.3 mmol, 2.0 equiv.) and imidazole (89 mg, 1.3 mmol, 2.0 equiv.) were added as solid to the solution. The flask was placed in a heated oil bath for 15 hours, the oil bath was removed, and the solution was diluted with aqueous saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford the bicyclic compound **2.57** (189 mg, 79%) as pale yellow oil.

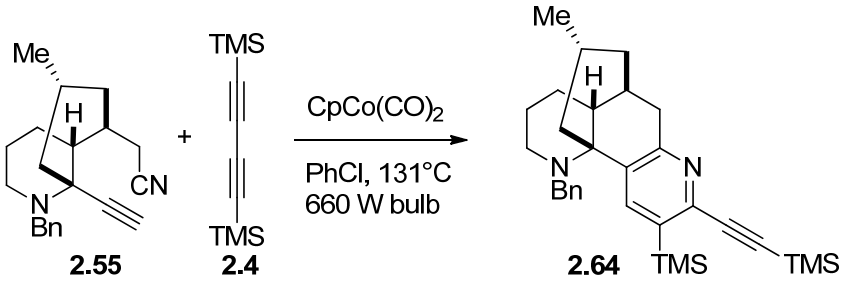
2.57: $[\alpha]^{23.0}_{D}$ -36.0° (*c* 0.50, CH_2Cl_2); R_f = 0.25 (silica gel, hexanes/EtOAc = 4/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.11 (t, *J* = 4.0 Hz, 1H), 1.29-1.37 (m, 1H), 1.41-1.51 (m, 2H), 1.58-1.66 (m, 2H), 1.71-1.76 (m, 1H), 1.93-2.00 (m, 2H), 2.11-2.15 (m, 1H), 2.23-2.30 (m, 2H), 2.50 (s, 1H), 2.55-2.63 (m, 2H), 2.87 (d, *J* = 17.0 Hz, 1H), 3.00 (dd, J = 12.0 and 17.2 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.01 (d, *J* = 13.6 Hz, 1H), 6.77-6.85 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3, 22.2, 24.3, 25.9, 26.7, 37.2, 38.1, 45.8, 46.4, 48.3, 53.0, 55.8, 55.9, 58.6, 76.6, 83.6, 110.8, 111.5, 120.4, 120.5, 132.8, 147.7, 148.8; **IR**: *v* 3278, 2921, 1612, 1504 cm^{-1}; **HRMS** calcd. for $C_{23}H_{31}N_2O_2^+$ [M +H^+]:367.2386. Found: 367.2380.



In a pressure tube 1,4-(bistrimethylsilyl)butdiyne **2.4** (317 mg, 1.6 mmol, 2.0 equiv.) and alkyne-nitrile **2.55** (250 mg, 0.82 mmol, 1.0 equiv.) were dissolved in freshly degassed THF (17 mL). Neat $CpCo(CO)_2$ (100 □L, 0.82 mmol, 1.0 equiv.) was added to the solution and the tube was sealed. The resulting solution was placed in a 140 °C oil bath and after 20 hours the vessel was cooled to 23 °C and the solvent was removed. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford **2.64** (320 mg, 78%) and **2.63** (12.3 mg, 3% yield).

2.64: $[\alpha]^{24}_{D}$ +5.0° (*c* 0.28, CH_2Cl_2); R_f = 0.60 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (s, 9H), 0.42 (s, 9H), 0.74 (d, *J* = 6.0 Hz, 3H), 1.13-1.32 (m, 5H), 1.44-1.46 (m, 2H), 1.53-1.61 (m, 1H), 1.69-1.77 (m, 1H), 1.85-1.90 (m, 1H), 2.07-2.10 (m, 1H), 2.37-2.44 (m, 1H), 2.48-2.53 (m, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 3.17 (dd, *J* = 14.8 and 18.8 Hz, 1H), 4.14 (dd, *J* = 14.4 and 60.0 Hz, 2H), 7.22-7.26 (m, 1H), 7.32-7.36 (m, 2H), 7.46-7.48 (m, 2H), 8.25 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.4, -0.4, 21.3, 22.3, 26.4, 27.0, 33.9, 35.2, 38.8, 43.7, 46.1, 48.1, 51.0, 60.3, 95.5, 106.0, 126.4, 127.8, 128.2, 134.9, 137.3, 140.2, 142.6, 144.1, 159.2; **IR**: *v* 1248, 842 cm^{-1}; **HRMS** calcd. for $C_{31}H_{45}N_2Si_2^+$ [M +H^+]: 501.31213. Found: 501.31193.

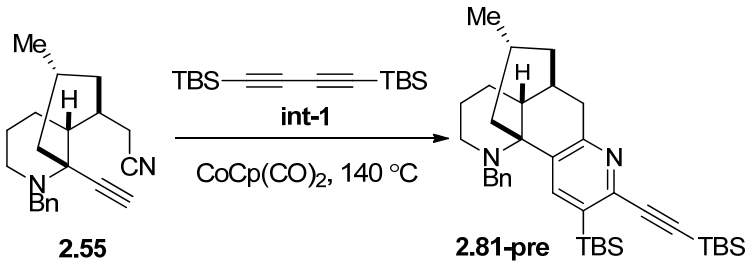
2.72: R_f = 0.55 (silica gel, silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.29 (s, 9H), 0.75 (d, *J* = 6.4 Hz, 3H), 0.83-0.88 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 1H), 1.14-1.21 (m, 1H), 1.2-1.33 (m, 2H), 1.42-1.61 (m, 2H), 1.72-1.80 (m, 2H), 1.89-1.94 (m, 1H), 2.09-2.12 (m, 1H), 2.4-2.52 (m, 2H), 3.19 (dd, *J* = 6.8 and 19.6 Hz, 1H), 4.14 (dd, *J* = 14.0 and 63.6 Hz, 2H), 7.24-7.33 (m, 1H), 7.34-7.50 (m, 2H), 7.48-7.50 (m, 2H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H); **IR**: *v* 2949, 2924, 1451, 1249, 843 cm^{-1}; **HRMS** calcd. for $C_{28}H_{37}N_2Si^+$ $[M+H]^+$: 429.27260. Found: 429.27203.



2.55 **2.4** **2.64**

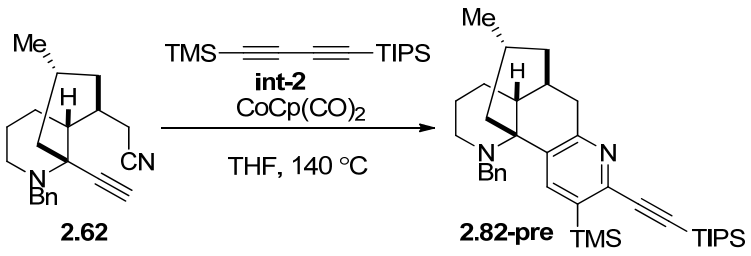
To alkyne-nitrile **2.55** (62 mg, 0.20 mmol, 1.0 equiv.) and diyne **2.4** (50 mg, 0.26 mmol, 1.3 equiv.) in degassed chlorobenzene (3 mL) was added a solution of $CoCp(CO)_2$ (0.049 mL, 0.40 mmol, 2 equiv.) in degassed chlorobenzene (2.5 mL) over 90 minutes. During the addition the reaction was irradiated with a 600 W slide projector lamp placed 5 cm from the flask. After four hours another portion of diyne **2.72** (50 mg, 0.26 mmol, 1.3 equiv.) was added in one portion. Irradiation continued for four hours. The reaction was loaded on a column and purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford compound **2.64** (71 mg, 70%).

Compound data: see above for **2.64**.



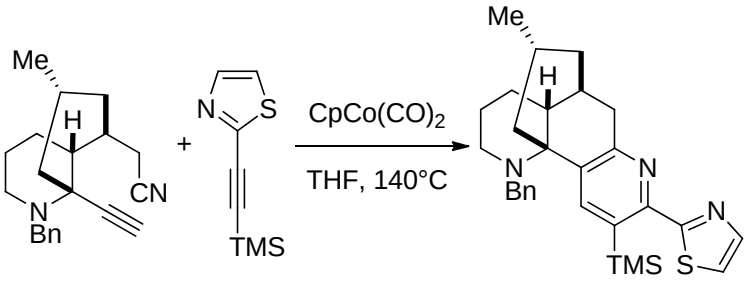
In a 30 mL pressure tube, 1,4-(bistrimethylsilyl)butdiyne **int-1** (455 mg, 1.63 mmol, 2.0 equiv.) and nitrile **2.55** (250 mg, 0.82 mmol, 1 equiv.) were dissolved in freshly degassed THF (17 mL). Neat $CpCo(CO)_2$ (0.2mL, 1.6 mmol, 2 equiv.) was added into the solution and the tube was sealed. The resulting solution was heated at 140 °C for 20h. The mixture was cooled to 23 °C and the solvent was evaporated. The crude material was purified by silica gel chromatography (0/1 to 1/5 EtOAc/Hexanes) to afford compound **2.81-pre** (300 mg, 63%) as dark brown foam.

2.81-pre: $[\alpha]^{23.0}_{D}$ +4.9° (*c* 0.23, CH_2Cl_2); R_f = 0.65 (silica gel, Hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.43 (s, 3H), 0.45 (s, 3H), 0.55 (d, *J* = 3.6 Hz, 3H), 0.80-0.99 (m, 20H), 1.12-1.30 (m, 2H), 1.36-1.45 (m, 1H), 1.51-1.75 (m, 2H), 1.86-1.89 (m, 1H), 2.02-2.09 (m, 1H), 2.35-2.50 (m, 2H), 2.66-2.79 (m, 1H), 3.13-3.21 (m, 1H), 4.02 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 7.20-7.25 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 8.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.5, 14.1, 16.9, 18.2, 21.1, 22.4, 26.4, 26.9, 27.1, 34.0, 35.1, 38.5, 43.6, 46.0, 48.3, 50.9, 60.2, 86.7, 92.7, 107.9, 126.4, 127.8, 128.2, 132.2, 136.7, 141.9, 142.5, 144.5, 159.2; **IR**: *v* 2926, 2856, 1507, 901 cm^{-1}; **HRMS** calcd. for $C_{31}H_{45}N_2Si_2^+$ [M +H^+]: 585.4060. Found: 585.4056.



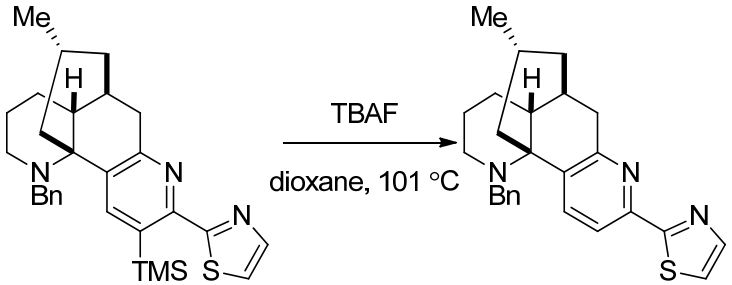
In a 12 mL pressure tube, 1,4-(bistrimethylsilyl)butdiyne **int-2** (34.1 mg, 0.12 mmol, 2.5 equiv.) and nitrile **2.55** (15 mg, 0.049 mmol, 1 equiv.) were dissolved in freshly degassed THF (1.5 mL). Neat $CpCo(CO)_2$ (9 μL, 0.073 mmol, 1.5 equiv.) was added into the solution and the tube was sealed. The resulting solution was heated at 140 °C for 36 h. The mixture was cooled to 23 °C and the solvent was evaporated. The crude material was purified by silica gel chromatography (0/1 to 1/5 EtOAc/Hexanes) to afford compound **2.82-pre** (14.9 mg, 52%) as dark brown foam.

2.82-pre: $[\alpha]^{23.0}_{D}$ +6.0° (*c* 0.33, CH_2Cl_2); R_f = 0.70 (silica gel, Hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.43 (s, 9H), 0.75 (d, *J* = 6.0 Hz, 3H), 1.05-1.32 (m, 23H), 1.44-1.48 (m, 2H), 1.50-1.56 (m, 1H), 1.69-1.80 (m, 2H), 1.84-1.90 (m, 1H), 2.06-2.11 (m, 1H), 2.37-2.52 (m, 2H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.17 (dd, *J* = 7.2 and 18.4 Hz, 1H), 4.07 (d, *J* = 14.4 Hz, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 7.22-7.26 (m, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 8.24 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.1, 11.6, 18.7, 21.3, 22.4, 26.4, 27.0, 34.0, 35.1, 38.9, 43.7, 46.0, 48.1, 51.0, 60.3, 91.8, 108.0, 126.4, 127.8, 128.2, 134.2, 137.0, 140.2, 142.7, 144.4, 159.3; **IR**: *v* 2944, 2865, 1493, 735 cm^{-1}; **HRMS** calcd. for $C_{37}H_{57}N_2Si_2^+$ [M +H^+]: 585.40603. Found: 585.40510.



2.55 **int-3** **2.107**

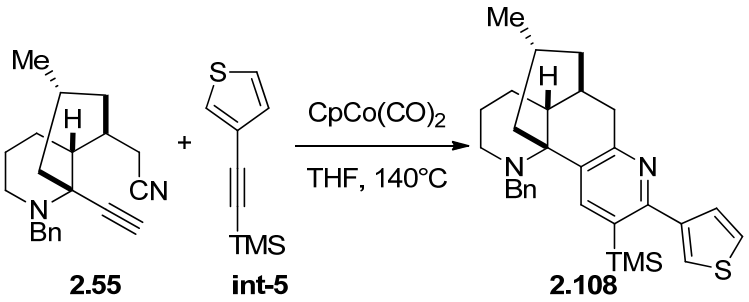
In a pressure tube **int-3** (18 mg, 98 μmol, 3.0 equiv.) and alkyne-nitrile **2.55** (10 mg, 33 μmmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmmol, 1.7 equiv.) was added to the solution and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 36 hours the vessel was removed from the oil bath, cooled to 23 °C, and the solution was concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford **2.107** (9.9 mg, 62%) as yellow oil.



2.107 **int-4**

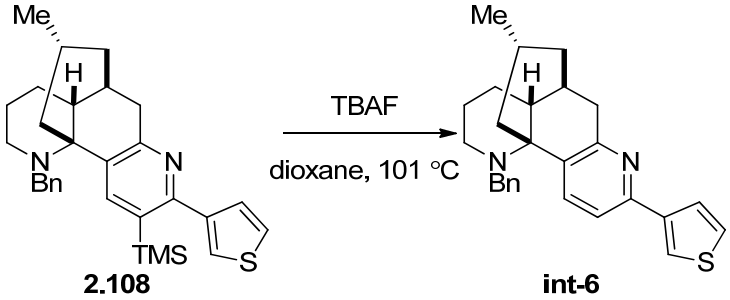
To a solution of **2.107** (9.9 mg, 20 μmol, 1.0 equiv.) in dioxane (1.0 mL) at 23 °C was added TBAF solution (81 μL, 1 M in THF, 81 μmol, 4.0 equiv.) and the resulting solution was placed in a heated oil bath. After 8 hours the mixture was cooled to 23 °C and concentrated. The crude material was purified on silica gel chromatography (1/0 to 5/1 hexanes/EtOAc) to afford **int-4** (5.9 mg, 70%) as light brown foam.

Int-4: $\mathbf{R}_f$ = 0.31 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 0.75 (d, J = 6.0 Hz, 3H), 1.13-1.16 (m, 1H), 1.20-1.34 (m, 4H), 1.47-1.59 (m, 2H), 1.74-1.81 (m, 2H), 1.93 (dt, J = 3.2 and 12.7 Hz, 1H), 2.11-2.14 (m, 1H), 2.44-2.60 (m, 2H), 2.74 (d, J = 18.6 Hz, 1H), 3.23 (dd, J = 3.2 and 18.6 Hz, 1H), 4.07 (d, J = 14.1 Hz, 1H), 4.22 (d, J = 14.1 Hz, 1H), 7.22-7.24 (m, 1H), 7.33-7.37 (m, 3H), 7.47 (d, J = 7.1 Hz, 2H), 7.88 (d, J = 3.3 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H); **^{13}C NMR** (150.8 MHz, $CDCl_3$): δ 21.1, 22.4, 26.5, 27.1, 34.0, 35.3, 38.5, 43.7, 45.9, 48.1, 50.9, 60.6, 117.6, 120.6, 126.5, 128.0, 128.3, 135.4, 139.8, 142.2, 143.9, 148.5, 158.7, 170.0; **IR**: ν 2923, 1384 cm^{-1}; **HRMS** calcd. for $C_{26}H_{30}N_3S^+$ [M +H$^+$]: 416.21550. Found: 416.21562.



2.55 **int-5** **2.108**

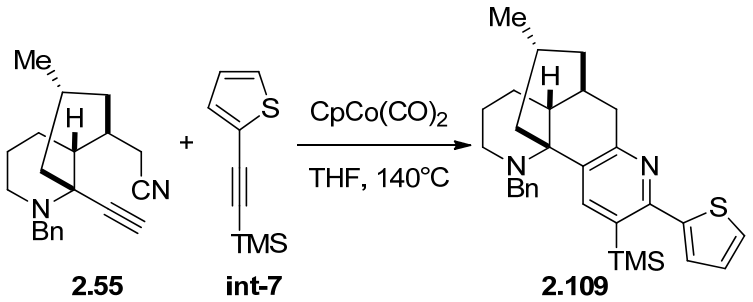
In a pressure tube **int-5** (17 mg, 98 μmol, 3.0 equiv.) and alkyne-nitrile **2.55** (10 mg, 33 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 30 hours the vessel was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford **2.108** (7.2 mg, 45%) as pale yellow oil.



2.108 **int-6**

To a solution of **2.108** (6.9 mg, 14 μmol, 1.0 equiv.) in dioxane (1.0 mL) at 23 °C was added TBAF solution (43 μL, 1 M in THF, 43 μmol, 3.0 equiv.) and the resulting solution was placed in a heated oil bath. After 8 hours the mixture was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (1/0 to 10/1 hexanes/EtOAc) to afford **int-6** (5.1 mg, 87%) as light brown foam.

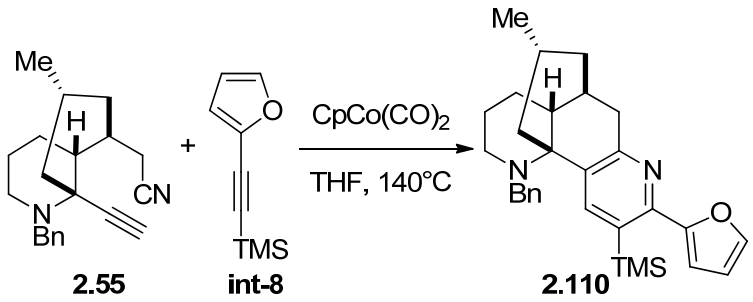
Int-6: $\mathbf{R}_f$ = 0.35 (silica gel, Hexanes/EtOAc = 5/1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 0.74 (d, J = 5.9 Hz, 3H), 0.82-0.88 (m, 1H), 1.12-1.16 (m, 1H), 1.23-1.29 (m, 2H), 1.30-1.38 (m, 1H), 1.44-1.57 (m, 2H), 1.72-1.78 (m, 2H), 1.90 (dt, J = 3.2 and 12.7 Hz, 1H), 2.09-2.11 (m, 1H), 2.48-2.50 (m, 2H), 2.72 (d, J = 18.6 Hz, 1H), 3.20 (dd, J = 7.0 and 18.6 Hz, 1H), 4.06 (d, J = 14.2 Hz, 1H), 4.22 (d, J = 14.2 Hz, 1H), 7.07 (dd, J = 3.4 and 5.0 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.31-7.35 (m, 3H), 7.46 (d, J = 7.3 Hz, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 1.1 and 3.4 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H); **^{13}C NMR** (150.8 MHz, $CDCl_3$): δ 21.1, 22.4, 26.5, 27.1, 34.1, 35.4, 38.6, 43.8, 45.9, 48.2, 50.9, 60.4, 117.0, 124.0, 126.5, 126.7, 127.9, 128.0, 128.2, 135.1, 136.8, 142.4, 145.4, 149.7, 158.5; **IR**: ν 2919, 1384 cm^{-1}; **HRMS** calcd. for $C_{27}H_{31}N_2S^+$ [M +H$^+$]: 415.2208. Found: 415.2208.



2.55 **int-7** **2.109**

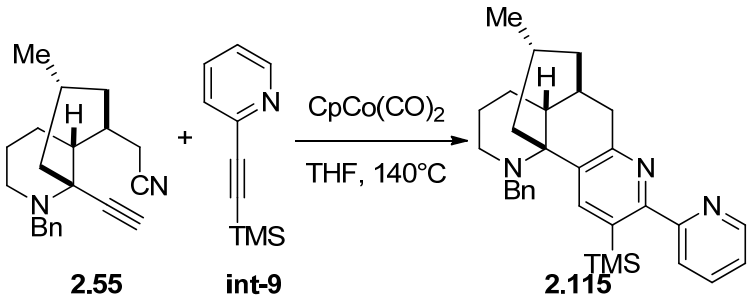
In a pressure tube **int-7** (16.1 mg, 89 μmol, 3.0 equiv.) and alkyne-nitrile **2.55** (9.1 mg, 30 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmmol, 1.8 equiv.) was added and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 30 hours the vessel was removed from the oil bath, cooled to 23 °C, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford **2.109** (8.9 mg, 51%) as pale yellow oil.

2.109: $\mathbf{R}_f$ = 0.65 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.11 (s, 9H), 0.78 (d, J = 5.6 Hz, 3H), 1.18-1.40 (m, 5H), 1.45-1.58 (m, 3H), 1.76-1.81 (m, 2H), 1.91 (dt, J = 3.6 and 13.2 Hz, 1H), 2.10-2.12 (m, 1H), 2.53 (d, J = 6.8 Hz, 1H), 2.71 (d, J = 19.2 Hz, 1H), 3.19 (dd, J = 6.8 and 19.2 Hz, 1H), 4.14 (d, J = 14.4 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 7.23-7.26 (m, 2H), 7.30-7.34 (m, 4H), 7.50 (d, J = 7.8 Hz, 2H), 8.34 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.22, 21.6, 22.5, 26.4, 27.1, 34.1, 35.3, 39.3, 43.8, 45.9, 48.1, 51.2, 60.2, 124.1, 125.0, 126.4, 127.8, 128.2, 129.1, 130.7, 135.3, 141.5, 142.7, 144.7, 157.5, 158.2; **IR**: ν 2923, 1428 cm^{-1}; **HRMS** calcd. for $C_{30}H_{39}N_2SSi^+$ [M +H^+]: 487.25977. Found: 487.25969.



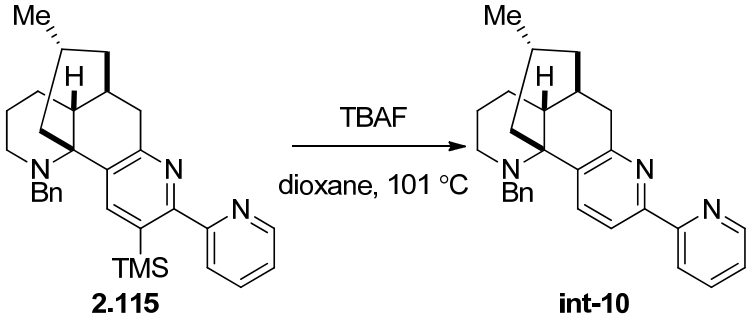
In a 10 mL pressure tube **int-8** (16.2 mg, 99 μmol, 3.0 equiv.) and alkyne-nitrile **2.55** (10.1 mg, 33 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 26 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford compound **2.110** (7.9 mg, 51%) as yellow oil.

2.110: $\mathbf{R}_f$ = 0.60 (silica gel, Hexanes/EtOAc = 2/1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.30 (s, 9H), 0.76 (d, J = 6.0 Hz, 3H), 1.17-1.37 (m, 4H), 1.44-1.80 (m, 4H), 1.86-1.92 (m, 1H), 2.11-2.13 (m, 1H), 2.47-2.55 (m, 2H), 2.71 (d, J = 9.5 Hz, 1H), 3.19 (dd, J = 7.3 and 18.8 Hz, 1H), 4.13 (d, J = 14.4 Hz, 1H), 4.24 (d, J = 14.4 Hz, 1H), 6.53 (dd, J = 1.7 and 3.2 Hz, 1H), 6.92 (d, J = 3.2 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 2H), 7.50 (d, J = 7.3 Hz, 3H), 8.38 (s, 1H); **^{13}C NMR** (125.6 MHz, $CDCl_3$): δ 0.38, 21.6, 22.4, 26.4, 27.1, 34.1, 35.3, 39.3, 43.8, 46.0, 48.1, 51.1, 60.3, 109.0, 112.1, 126.4, 127.8, 128.2, 129.0, 135.7, 141.6, 142.1, 142.7, 151.0, 155.8, 158.5; **IR**: ν 3393, 2918, 1384 cm^{-1}; **HRMS** calcd. for $C_{30}H_{39}N_2OSi^+$ [M +H^+]: 471.28262. Found: 471.28291.



2.55 **int-9** **2.115**

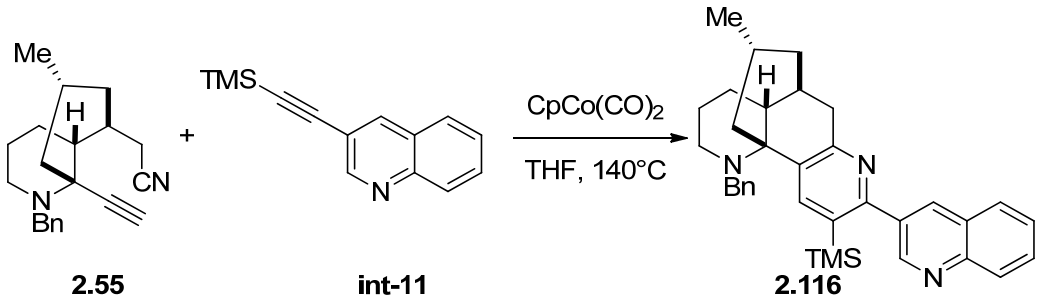
In a pressure tube **int-9** (17.2 mg, 98 μmol, 3.0 equiv.) and alkyne-nitrile **2.55** (10 mg, 33 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (1.5 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 24 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 2/1 hexanes/EtOAc) to afford **2.115** (8.2 mg, 52%) as yellow oil.



2.115 **int-10**

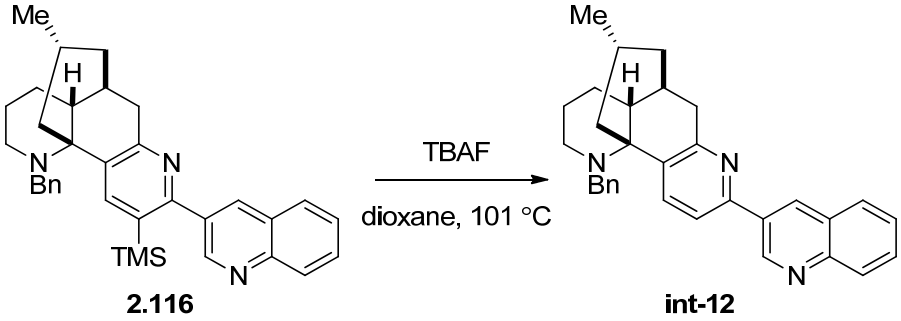
To a solution of alkyne **2.115 (**8.2 mg, 17 μmol, 1 equiv.) in dioxane (1.0 mL) at 23 °C was added TBAF solution (49 μL, 1 M in THF, 49 μmol, 3.0 equiv.) and the resulting solution was placed in a heated oil bath. After 14 hours the mixture was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (20/1 to 1/1 hexanes/EtOAc) to afford **int-10** (6.1mg, 88%) as light brown foam.

Int-10: $\mathbf{R}_f$ = 0.35 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.68 (d, J = 6.0 Hz, 3H), 0.78-0.83 (m, 1H), 1.08-1.54 (m, 6H), 1.71-1.75 (m, 2H), 1.89 (d, J = 3.6 and 8.8 Hz, 1H), 2.07-2.09 (m, 1H), 2.45-2.47 (m, 2H), 2.72 (d, J = 18.8 Hz, 1H), 3.21 (dd, J = 7.2 and 18.8 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 4.18 (d, J = 14.0 Hz, 1H), 7.16-7.22 (m, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.72 (dt, J = 1.6 and 7.6 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.27 (dt, J = 1.2 and 7.6 Hz, 1H), 8.60-8.63 (m, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$): δ 21.3, 22.4, 26.5, 27.2, 34.2, 35.6, 38.8, 43.8, 45.9 48.2, 51.1, 60.5, 119.1, 121.0, 123.2, 126.5, 128.0, 128.8, 135.3, 136.7, 138.6, 142.4, 149.2, 153.4, 156.8, 158.1; **IR**: ν 2919, 1384 cm^{-1}; **HRMS** calcd. for $C_{28}H_{32}N_3^+$ [M +H$^+$]: 410.25907. Found: 410.25875.



2.55 **int-11** **2.116**

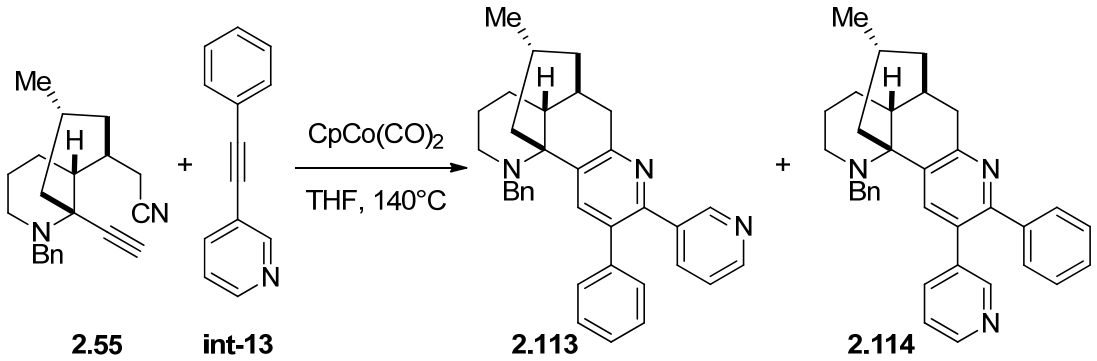
In a 10 mL pressure tube **int-11** (21.6 mg, 96 µmol, 3.0 equiv.) and alkyne-nitrile **2.55** (9.8 mg, 33 µmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (8 µL, 57 µmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 36 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 2/1 EtOAc/Hexanes) to afford compound **2.116** (4.9 mg, 28%) as yellow oil.



2.116 **int-12**

To a solution of **2.116 (**4.9 mg, 9.2 µmol, 1.0 equiv.) in dioxane (1.0 mL) at 23 °C was added TBAF solution (1 M in THF, 37 µL, 37 µmol, 4.0 equiv.) and the resulting solution was placed in a heated oil bath. After 14 hours the mixture was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (20/1 to 1/1 hexanes/EtOAc) to afford compound **int-12** (4.0 mg, 94%) as light brown foam.

Int-12: $\mathbf{R}_f$ = 0.43 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.79 (d, J = 5.9 Hz, 3H), 0.83-0.90 (m, 1H), 1.18-1.44 (m, 4H), 1.52-1.59 (m, 2H), 1.78-1.88 (m, 2H), 1.98 (dt, J = 3.7 and 16.1 Hz, 1H), 2.17-2.20 (m, 1H), 2.54-2.57 (m, 2H), 2.84 (d, J = 18.5 Hz, 1H), 3.33 (dd, J = 7.1 and 18.5 Hz, 1H), 4.11 (d, J = 14.2 Hz, 1H), 4.28 (d, J = 14.2 Hz, 1H), 7.24-7.27 (m, 1H), 7.36-7.47 (m, 2H), 7.50 (d, J = 10.0 Hz, 2H), 7.58-7.59 (m, 1H), 7.71-7.76 (m, 2H), 7.93-7.95 (m, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H), 9.55 (d, J = 2.1 Hz, 1H); **^{13}C NMR** (150.8 MHz, $CDCl_3$): δ 21.1, 22.4, 26.6, 27.2, 34.1, 35.6, 38.6, 43.8, 45.9, 48.2, 51.0, 60.5, 118.9, 126.5, 126.8, 128.0, 128.3, 128.5, 129.0, 129.6, 129.7, 132.4, 133.6, 135.5, 137.8, 142.3, 148.0, 149.6, 151.8, 159.3; **IR**: ν 2917, 1384 cm^{-1}; **HRMS** calcd. for $C_{32}H_{34}N_3^+$ [M +H$^+$]: 460.27472. Found: 460.27503.

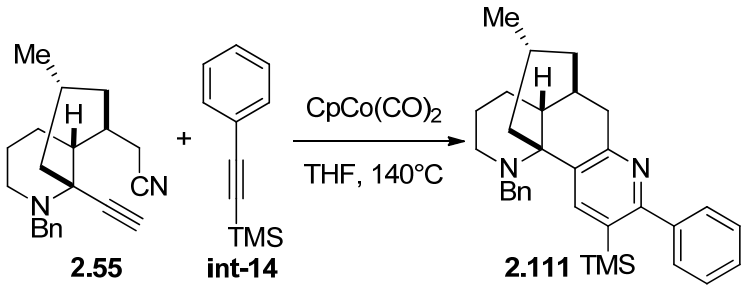


2.55 **int-13** **2.113** **2.114**

In a pressure tube **int-13** (23 mg, 0.13 mmol, 2.6 equiv.) and alkyne-nitrile **2.55** (15 mg, 49 µmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.5 mL). Neat $CpCo(CO)_2$ (10 µL, 82 µmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 14 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 1/1 hexanes/EtOAc) to afford **2.113** (6.9 mg, 26%) and **2.114** (3.0mg, 16%).

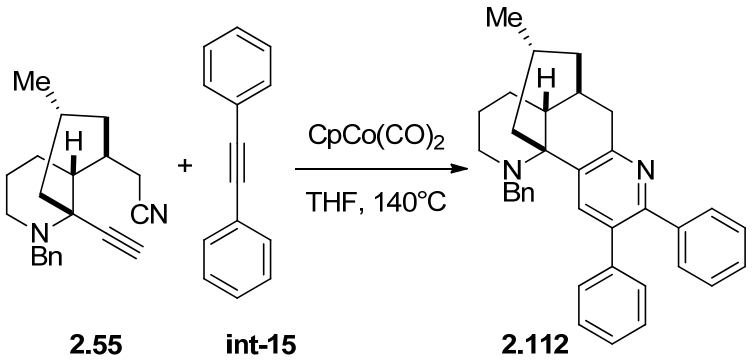
2.113: $\mathbf{R}_f$ = 0.31 (silica gel, Hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.81 (d, J = 5.6 Hz, 3H), 0.86-0.95 (m, 1H), 1.21-1.60 (m, 6H), 1.81-1.83 (m, 3 H), 1.96-2.00 (m, 2H), 2.17-2.18 (m, 1H), 2.54-2.65 (m, 2H), 2.79 (d, J = 18.8 Hz, 1H), 3.30 (dd, J = 7.6 and 18.8 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.15-7.34 (m, 7H), 7.45 (d, J = 7.6 Hz, 2H), 7.69 (dt, J = 2.0 and 7.6 Hz, 1H), 8.16 (s, 1H), 8.47 (dd, J = 2.0 and 4.8 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.5, 22.4, 26.5, 27.1, 34.0, 35.3, 38.9, 43.7, 45.9, 48.1, 51.1, 60.4, 122.7, 126.5, 127.2, 128.0, 128.2, 128.3, 128.5, 129.7, 134.4, 136.2, 136.8, 137.2, 137.6, 139.8, 142.2, 148.3, 150.9, 158.0; **IR**: ν 2919, 1384 cm^{-1}; **HRMS** calcd. for $C_{34}H_{36}N_3^+$ [M +H^+]: 486.29037. Found: 486.29099.

2.114: $\mathbf{R}_f$ = 0.69 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.82 (d, J = 6.0 Hz, 3H), 1.21-1.46 (m, 5H), 1.46-1.62 (m, 2H), 1.81-1.84 (m, 2H), 1.97-2.01 (m, 1H), 2.18-2.19 (m, 1H), 2.59-2.66 (m, 2H), 2.83 (d, J = 18.8 Hz, 1H), 3.32 (dd, J = 7.2 and 18.8 Hz, 1H), 7.13 (d, J = 14.4 Hz, 1H), 4.24 (d, J = 14.4 Hz, 1H), 7.16-7.27 (m, 6H), 7.32-7.35 (m, 4H), 7.42-7.46 (m, 2H), 8.13 (d, J = 2.0 Hz, 1H), 8.50-8.54 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.3, 22.4, 26.5, 27.1, 34.1, 35.3, 38.7, 43.7, 45.9, 48.2, 51.1, 60.4, 122.9, 126.5, 127.8, 128.0, 128.1, 128.3, 130.0, 130.2, 136.4, 136.5, 137.0, 137.0, 139.7, 142.1, 148.0, 150.2, 154.4, 158.4; **IR**: ν 2913, 1384 cm^{-1}; **HRMS** calcd. for $C_{34}H_{36}N_3^+$ [M +H^+]: 486.29037. Found: 486.29092.



In a pressure tube **int-14** (8.4 mg, 48 μmol, 4.1 equiv.) and alkyne-nitrile **2.55** (3.6 mg, 12 μmmol, 1.0 equiv.) were dissolved in freshly degassed THF (1 mL). Neat $CpCo(CO)_2$ (3 μL, 24 μmmol, 2.0 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 12 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 10/1 hexanes/EtOAc) to afford **2.111** (2.3 mg, 51%) as brown foam.

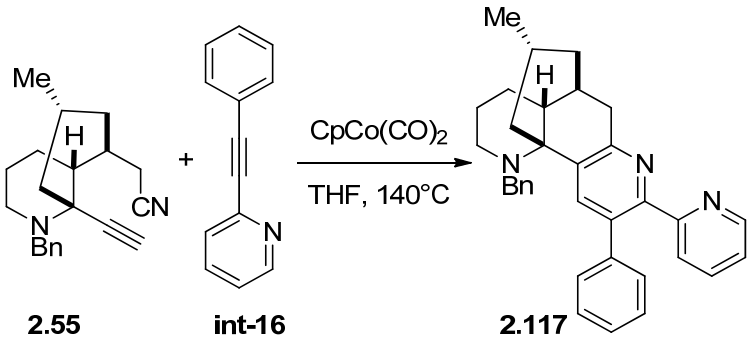
2.111: $\mathbf{R}_f$ = 0.65 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.06 (s, 9H), 0.79 (d, J = 5.6 Hz, 3H), 1.19-1.41 (m, 4H), 1.45-1.54 (m, 2H), 1.75-1.79 (m, 2H), 1.90-1.93 (m, 1H), 2.11-2.12 (m, 1H), 1.75-1.78 (m, 1H), 2.54-2.56 (m, 2H), 2.72 (d, J = 18.8 Hz, 1H), 4.12 (d, J = 14.4 Hz , 1H), 4.15 (d, J = 14.4 Hz, 1H), 4.26 (d, J = 14.4 Hz, 1H), 7.25-7.45 (m, 8H), 7.51 (d, J = 8.0 Hz, 2H), 8.34 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 0.2, 21.7, 22.5, 26.4, 27.1, 34.2, 35.4, 39.4, 43.8, 46.0, 48.2, 51.2, 60.2, 126.4, 127.7, 127.8, 127.9, 128.2, 129.1, 130.2, 135.0, 141.6, 142.8, 143.9, 158.0, 162.3; **IR**: ν 2918, 1384, 837 cm^{-1}; **HRMS** calcd. for $C_{32}H_{41}N_2Si^+$ [M +H$^+$]: 481.3039. Found: 481.3033.



2.55 **int-15** **2.112**

In a pressure tube **int-15** (25 mg, 0.14 mmol, 3.0 equiv.) and alkyne-nitrile **2.55** (14.5 mg, 47 µmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.2 mL). Neat $CpCo(CO)_2$ (10 µL, 82 µmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 30 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 10/1 hexanes/EtOAc) to afford **2.112** (9.9 mg, 43%) as pale yellow foam.

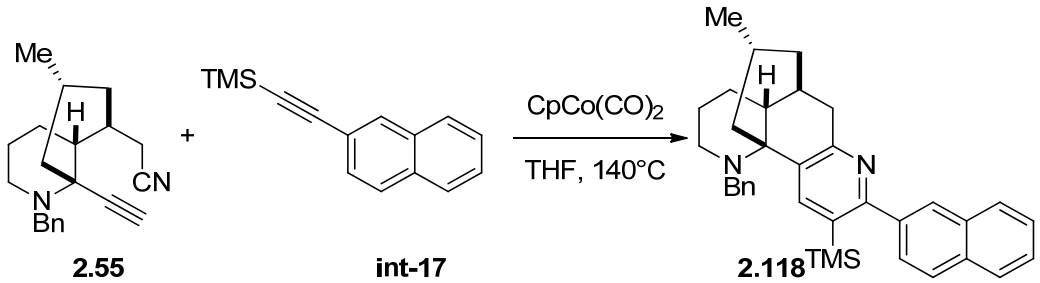
2.112: $\mathbf{R}_f$ = 0.45 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.81 (d, J = 6.0 Hz, 1H), 1.21-1.25 (m, 1H), 1.33-1.64 (m, 6H), 1.79-1.83 (m, 2H), 1.97 (dt, J = 3.2 and 12.4 Hz, 1H), 2.15-2.17 (m, 1H), 2.53-2.68 (m, 2H), 2.80 (d, J = 18.4 Hz, 1H), 3.30 (dd, J = 7.2 and 18.4 Hz, 1H), 4.16 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.21-7.38 (m, 13H), 7.46 (d, J = 7.2 Hz, 2H), 8.12 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.6, 22.5, 26.5, 27.1, 34.1, 35.3, 39.1, 43.8, 45.9, 48.1, 51.2, 60.3, 126.4, 126.7, 127.4, 127.8, 127.8, 127.9, 128.2, 129.7, 130.0, 133.8, 136.6, 136.6, 140.4, 140.7, 142.4, 154.0, 157.4; **IR**: ν 2922, 1384 cm^{-1}; **HRMS** calcd. for $C_{35}H_{37}N_2^+$ [M +H^+]: 485.2957. Found: 485.2959.



2.55 **int-16** **2.117**

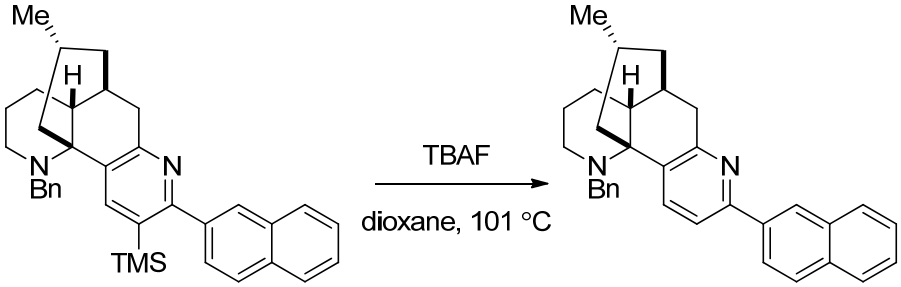
In a pressure tube **int-16** (23 mg, 0.13 mmol, 2.6 equiv.) and alkyne-nitrile **2.55** (15 mg, 49 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.5 mL). Neat $CpCo(CO)_2$ (10 μL, 82 μmol, 1.7 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 14 hours the vessel was cooled to 23 °C and the reaction was cooled. The crude material was purified by silica gel chromatography (20/1 → 1/1 hexanes/EtOAc) to afford **2.117** (6.9 mg, 26%) as pale foam.

2.117: $\mathbf{R}_f$ = 0.21 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.79 (d, J = 5.8 Hz, 3H), 1.22-1.60 (m, 6H), 1.73-1.79 (m, 3H), 1.95-1.99 (m, 1H), 2.16-2.17 (m, 1H), 2.53-2.67 (m, 2H), 2.85 (d, J = 15.6 Hz, 1H), 3.26-3.35 (m, 1H), 4.23 (s, 2H), 7.00 (d, J = 7.6 Hz, 1H), 7.15-7.38 (m, 9H), 7.44-7.49 (m, 3H), 8.34 (s, 1H), 8.70 (d, J = 4.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.9, 22.4, 26.4, 27.1, 34.1, 39.6, 43.8, 46.0, 47.9, 51.3, 60.4, 77.2, 121.6, 125.3, 126.4, 127.9, 128.0, 128.0, 128.1, 128.2, 129.9, 132.5, 135.5, 136.8, 142.4, 149.7, 152.8, 159.8; **IR**: ν 3423, 1918, 1384 cm^{-1}; **HRMS** calcd. for $C_{34}H_{36}N_3^+$ [M +H^+]: 486.29037. Found: 486.29031.



2.55 **int-17** **2.118**

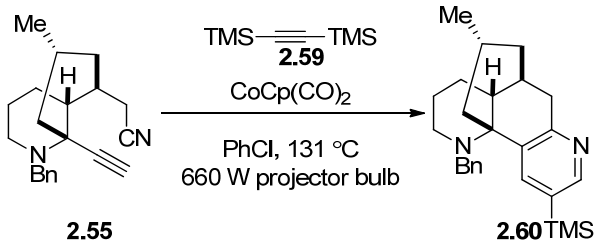
In a pressure tube **int-17** (22 mg, 0.10 mmol, 3.0 equiv.) and alkyne-nitrile **2.55** (10 mg, 33 μmol, 1.0 equiv.) were dissolved in freshly degassed THF (1.5 mL). Neat $CpCo(CO)_2$ (8 μL, 57 μmol, 1.9 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 36 hours the vessel was cooled to 23 °C and the reaction was concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford **2.118** (8.9 mg, 51%).



2.118 **int-18**

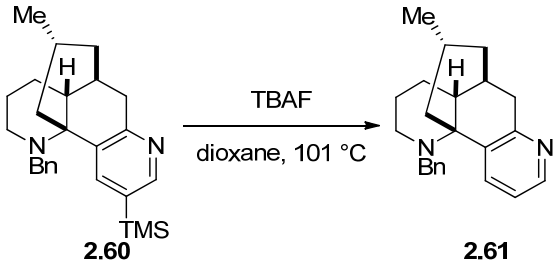
To a solution of **2.118** (8.9 mg, 17 μmol, 1.0 equiv.) in dioxane (1 mL) at 23 °C was added TBAF solution (80 μL, 1 M in THF, 0.080 mmol, 4.8 equiv.) and the resulting solution was placed in a heated oil bath. After four hours the mixture was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (1/0 to 20/1 hexanes/EtOAc) to afford **int-18** (7.2 mg, 94%) as light brown foam.

Int-18: $\mathbf{R}_f$ = 0.45 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.78 (d, J = 5.8 Hz, 3H), 0.86-0.90 (m, 1H), 1.18-1.46 (m, 4H), 1.50-1.63 (m, 3H), 1.79-1.83 (m, 1H), 1.96 (dt, J = 3.6 and 9.5 Hz, 1H), 2.16-2.18 (m, 1H), 2.55-2.59 (m, 2H), 2.82 (d, J = 18.3 Hz, 1H), 3.33 (dd, J = 3.6 and 18.3 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 4.27 (d, J = 14.1 Hz, 1H), 7.25-7.27 (m, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.47-7.52 (m, 3H), 7.73 (d, J = 8.2 Hz, 1H), 7.85-7.96 (m, 3H), 8.16 (dd, J = 1.8 and 8.2 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.49 (s, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$): δ 21.2, 22.4, 26.6, 27.2, 34.2, 35.7, 38.8, 43.9, 45.9, 48.2, 51.0, 60.4, 118.8, 124.8, 126.0, 126.1, 126.2, 126.5, 127.6 128.0, 128.2, 128.3, 128.7, 133.4, 133.6, 135.2, 136.9, 137.1, 142.5, 154.3, 158.7; **IR**: ν 2920, 1384 cm^{-1}; **HRMS** calcd. for $C_{33}H_{35}N_2^+$ [M +H^+]: 459.27948. Found: 459.27940.



In a pressure tube **2.55** (18 mg, 59 μmol, 1.0 equiv.) and bis TMS-alkyne **2.59** (33 mg, 0.19 mmol, 3.3 equiv.) were dissolved in freshly degassed chlorobenzene (0.5 mL). A solution of $CpCo(CO)_2$ (10 μL, 82 μmol, 1.4 equiv.) in chlorobenzene (0.5 mL) was added by syringe pump (0.5mL/h). The reaction was heated to reflux with a projector light for 2 hours. The mixture was cooled to 23 °C and the solvent was removed. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford compound **2.60** (6.1 mg, 26%) as dark brown oil.

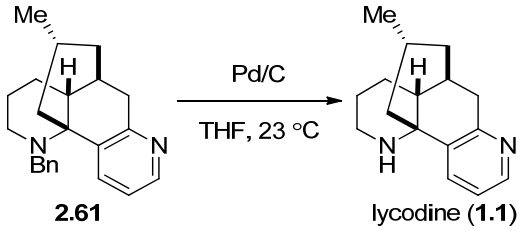
2.60: $[\alpha]^{23.0}_{D}$ +20.0° (*c* 0.35, CH_2Cl_2); R_f = 0.32 (silica gel, hexanes/EtOAc = 4/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.32 (s, 9H), 0.76 (d, *J* = 6.0 Hz, 3H), 1.15-1.34 (m, 4H), 1.41-1.58 (m, 3H), 1.74-1.78 (m, 2H), 1.90 (dt, *J* = 3.2 and 12.4 Hz, 1H), 2.09-2.12 (m, 1H), 2.41-2.53 (m, 2H), 2.67 (d, *J* = 18.8 Hz, 1H), 3.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.12 (d, *J* = 14.4 Hz, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 7.23-7.26 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.0, 22.6, 23.6, 27.5, 28.2, 35.1, 36.4, 40.2, 44.9, 47.0, 49.3, 52.3, 61.3, 127.6, 128.9, 129.3, 133.2, 138.3, 140.7, 143.8, 151.9, 160.0; **IR**: *v* 2919, 1360, 837 cm^{-1}; **HRMS** calcd. for $C_{26}H_{37}N_2Si^+$ [M +H$^+$]: 405.2726. Found: 405.2719.



2.60 **2.61**

To a solution of **2.60** (25 mg, 62 μmol, 1.0 equiv.) in THF (2 mL) at 23 °C was added TBAF solution (0.19 mL, 1 M in THF, 0.19 mmol, 3.0 equiv.) and the flask was immersed in a heated oil bath. After 12 hours the mixture was cooled to 23 °C and diluted with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 2/1 hexanes/EtOAc) to afford **2.61** (20 mg, 97%).

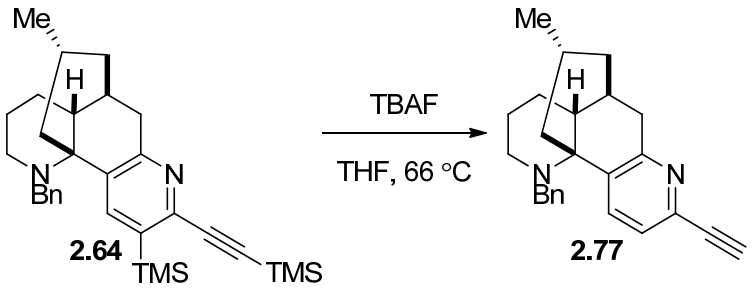
2.61: $[\alpha]^{23.0}_{D}$ +49.2° (*c* 0.63, CH_2Cl_2); R_f = 0.23 (silica gel, hexanes/EtOAc = 4/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.75 (d, *J* = 6.0 Hz, 3H), 1.13-1.36 (m, 5H), 1.44-1.50 (m, 1H), 1.55-1.59 (m, 1H), 1.73-1.81 (m, 2H), 1.92 (dt, *J* = 7.2 and 12.8 Hz, 1H), 2.10-2.13 (m, 1H), 2.43-2.52 (m, 2H), 2.68 (d, *J* = 18.8 Hz, 1H), 3.21 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 7.14 (dd, *J* = 4.8 and 8.0 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 8.12 (dd, *J* = 1.2 and 8.0 Hz, 1H), 8.38 (dd, *J* = 1.2 and 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 22.4, 26.5, 27.1, 34.0, 35.4, 38.5, 43.8, 45.5, 48.2, 50.9, 60.3, 121.6, 126.5, 128.0, 128.2, 134.4, 138.2, 142.4, 146.8, 158.6; **IR**: *v* 2919, 1359, 735 cm^{-1}; **HRMS** calcd. for $C_{23}H_{29}N_2^+$ [M +H^+]: 333.2331. Found: 333.2327.



2.61 lycodine (**1.1**)

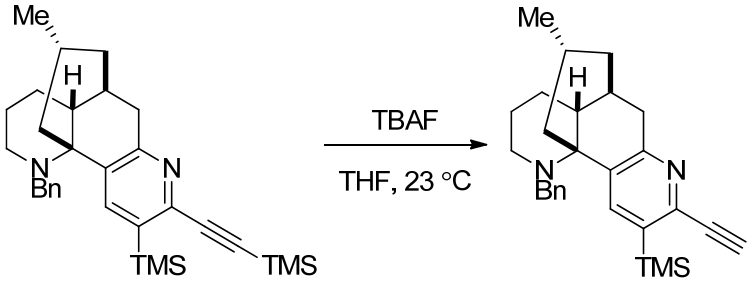
Lycodine (**1.1**): Under 1 atm H_2, pyridne **2.61** (4.2 mg, 0.044 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL) and Pd/C (1 mg, 10% wt, 7%) was added at 23 °C. After 10 hours the same amount of Pd/C was added. After another 10 hours, the reaction was diluted with EtOAc (10 mL), and filtered, concentrated to afford lycodine (**1.1**) (2.9 mg, 95%) as white crystal (**m.p.** : 95.3-96.3 °C).

Lycodine (**1.1**)**:** $[\alpha]^{23.0}_{D}$ -69.2° (*c* 0.13, MeOH); R_f = 0.22 (silica gel, $CHCl_3$/MeOH = 100/7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.81 (d, *J* = 6.4 Hz, 3H), 1.10-1.21 (m, 2H), 1.32 (m, 2H), 1.36-1.43 (m, 1H), 1.49 (ddd, *J* = 2.0, 3.6 and 12.0 Hz, 1H), 1.56-1.61 (m, 2H), 1.66 (dt, *J* = 3.6 and 12.8 Hz, 1H), 1.73 (dt, *J* = 3.6 and 12.8 Hz, 1H), 1.78-1.84 (m, 1H), 2.11-2.15 (m, 1H), 2.45 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.68 (d, *J* = 18.8 Hz, 1H), 2.75-2.80 (m, 1H), 3.15 (dd, *J* = 7.2 Hz, 1H), 7.29 (dd, *J* = 4.8 and 8.0 Hz, 1H), 7.89 (dd, *J* = 1.6 and 8.0 Hz, 1H), 8.31 (dd, *J* = 1.6 and 4.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.3, 27.0, 27.1, 27.4, 34.7, 35.7, 42.0, 44.5, 44.7, 51.5, 58.0, 123.3, 135.3, 137.3, 147.6, 159.6; **IR**: *v* 3438, 1635 cm^{-1}; **HRMS** calcd. for $C_{16}H_{23}N_2^+$ [M +H^+]: 243.1861. Found: 243.1856.



To a solution of **2.64** (700 mg, 1.3 mmol, 1.0 equiv.) in THF (15 mL) at 23 °C was added TBAF solution (6.0 mL, 1 M in THF, 6.0 mmol, 4.5 equiv.) and the flask was immersed in a heated oil bath. After 13 hours the mixture was cooled to 23 °C, diluted with saturated NH_4Cl solution (20 mL), and extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 to 5/1 hexanes/EtOAc) to afford **2.77** (431 mg, 85%) as light brown foam.

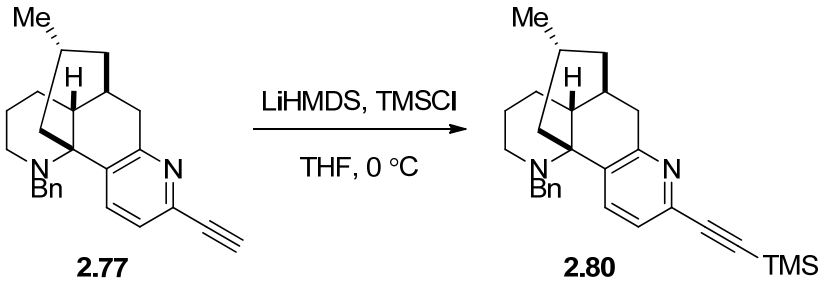
2.77: $[\alpha]^{24}_{D}$ +19.1° (*c* 0.29, CH_2Cl_2); R_f = 0.43 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.75 (d, *J* = 6.0 Hz, 3H), 1.11-1.32 (m, 4H), 1.47-1.58 (m, 3H), 1.74-1.80 (m, 2H), 1.91-1.94 (m, 1H), 2.05-2.12 (m, 1H), 2.37-2.53 (m, 2H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.10 (s, 1H), 3.22 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 4.21 (d, *J* = 14.0 Hz, 1H), 7.25-7.47 (m, 6H), 8.11 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.8, 22.4, 26.4, 27.1, 33.9, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 60.4, 76.1, 83.2, 125.4, 126.5, 128.0, 128.2, 134.6, 138.9, 139.0, 142.1, 159.3; **IR**: *v* 1559, 1451, 734 cm^{-1}; **HRMS** calcd. for $C_{25}H_{29}N_2^+$ $[M+H]^+$: 357.23307. Found: 357.23225.



2.64 **2.83**

To a solution of **2.72** (50 mg, 0.10 mmol, 1.0 equiv.) in THF (5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 0.15 mmol, 1.5 equiv.). After 10 minutes the mixture was diluted with aqueous saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 10/1 hexanes/EtOAc) to afford compound **2.83** (39 mg, 91%) as light yellow foam.

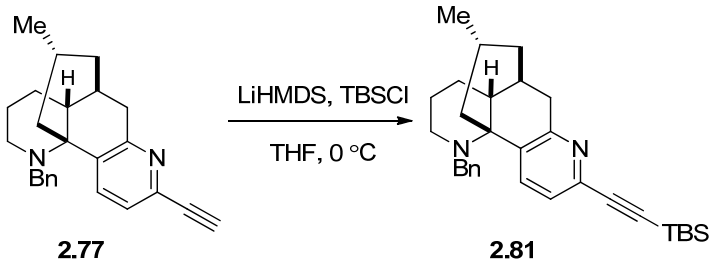
2.83: $\mathbf{R}_f$ = 0.55 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.42 (s, 9H), 0.75 (d, J = 6.4 Hz, 3H), 0.83-0.92 (m, 1H), 1.11-1.32 (m, 4H), 1.46 (s, 1H), 1.52-1.58 (m, 1H), 1.70-1.77 (m, 2H), 1.89 (dt, J = 3.6 and 12.8 Hz, 1H), 2.08-2.12 (m, 1H), 2.37-2.54 (m, 2H), 2.69 (d, J = 18.8 Hz, 1H), 3.14-3.20 (m, 2H), 4.07 (d, J = 14.4 Hz, 1H), 4.22 (d, J = 14.4 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.33-7.36 (m, 2H), 7.46-7.48 (m, 2H), 8.27 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.34, 21.3, 22.4, 26.3, 27.0, 33.9, 35.2, 38.8, 43.7, 46.0, 48.1, 51.0, 60.3, 78.1, 84.8, 126.5, 127.8, 128.2, 134.8, 137.6, 140.3, 142.5, 143.3, 159.3; **IR**: ν 2921, 1247, 841 cm^{-1}; **HRMS** calcd. for $C_{28}H_{37}N_2Si^+$ [M +H^+]: 429.2726. Found: 429.2722.



2.77 **2.80**

To a solution of **2.77** (600 mg, 1.7 mmol, 1.0 equiv.) in THF (15 mL) at 0 °C was added a solution of LiHMDS (2.0 mL, 1.0 M in THF, 2.0 mmol, 1.2 equiv.) dropwise over two minutes. After 10 minutes neat TMSCl (0.30 mL, 2.4 mmol, 1.4 equiv.) was added. The resulting solution was stirred for one hour, diluted with aqueous saturated NH_4Cl solution (20 mL), and extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford alkyne **2.80** (650 mg, 90%) as light brown foam.

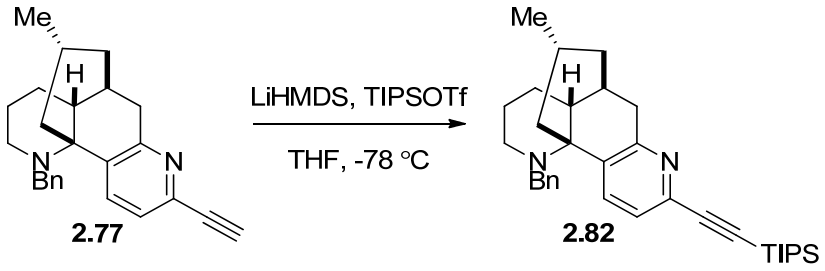
2.80: $[\alpha]^{24}_{D}$ +73.9° (*c* 1.9, CH_2Cl_2); R_f = 0.65 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (s, 9H), 0.73 (d, *J* = 6.4 Hz, 3H), 1.11-1.32 (m, 4H), 1.43-1.61 (m, 3H), 1.72-1.82 (m, 2H), 1.91 (dt, *J* = 3.6 and 12.4 Hz, 1H), 2.09-2.11 (m, 1H), 2.36-2.53 (m, 2H), 2.70 (d, J =18.8 Hz, 1H), 3.18 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.3 (d, *J* = 14.0 Hz, 1H), 4.21 (d, *J* = 14.0 Hz, 1Hc c), 7.23-7.46 (m, 6H), 8.07 (d, *J* = 1.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -0.2, 20.8, 22.3, 26.4, 27.1, 33.9, 35.4, 38.2, 43.7, 45.7, 48.1, 50.8, 60.4, 93.5, 104.2, 125.5, 126.5, 128.0, 128.2, 134.5, 138.5, 139.9, 142.2, 159.2; **IR**: *v* 1434, 1249, 843 cm^{-1}; **HRMS** calcd. for $C_{28}H_{37}N_2Si^+$ $[M+H]^+$: 429.27260. Found: 429.27143.



2.77 **2.81**

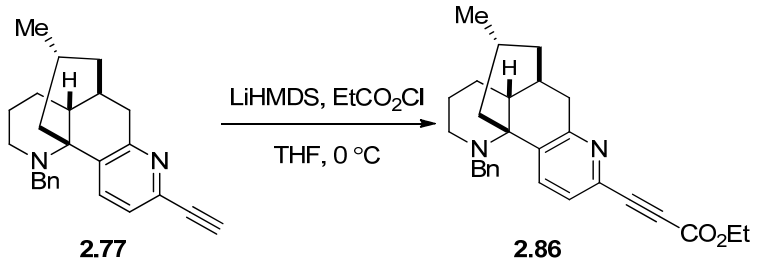
To a solution of **2.77** (9.0 mg, 25 μmol, 1.0 equiv.) in THF (1.0 mL) at 0 °C was added LiHMDS solution (80 μL, 1.0 M in THF/toluene, 0.080 mmol, 3.2 equiv.) followed by solid TBSCl (6.6 mg, 44 μmol, 1.7 equiv.). After three hours the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 10/1 hexanes/EtOAc) to afford **2.81** (10.1 mg, 85%) as clear oil.

2.81: $[\alpha]^{23.0}_{D}$ +43.3° (*c* 0.30, CH_2Cl_2); R_f = 0.75 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.74 (d, *J* = 3.0 Hz, 3H), 1.01 (s, 9H), 1.11-1.32 (m, 4H), 1.43-1.49 (m, 1H), 1.54-1.59 (m, 2H), 1.64 (brs, 1H), 1.72-1.80 (m, 2H), 1.91 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.09-2.11 (m, 1H), 2.37-2.53 (m, 2H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.02 (d, *J* = 19.2 Hz, 1H), 4.20 (d, *J* = 19.2 Hz, 1H), 7.22-7.25 (m, 1H), 7.32-7.40 (m, 2H), 7.44-7.47 (m, 2H), 8.08 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.68, 16.7, 20.9, 22.3, 26.2, 26.5, 27.1, 33.9, 35.3, 38.2, 43.7, 45.7, 48.1, 50.8, 60.4, 92.0, 105.0, 125.8, 126.5, 128.0, 128.2, 134.4, 138.4, 140.0, 142.2, 159.1; **IR**: *v* 2925, 1449, 1384 cm^{-1}; **HRMS** calcd. for $C_{31}H_{43}N_2Si^+$ [M +H^+]: 471.3196. Found: 471.3191.



To a solution of **2.77** (14.5 mg, 41 μmol, 1.0 equiv.) in THF (1 mL) at –78 °C was added LiHMDS solution (61 μL, 1.0 M in THF/toluene, 61 μmol, 1.5 equiv.) and neat TIPSOTf (12 μL, 45 μmol, 1.1 equiv.). After one hour the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 10/1 hexanes/EtOAc) to afford **2.77** (4.2 mg, 20%) as clear oil and **2.82** (4.9 mg, 33%).

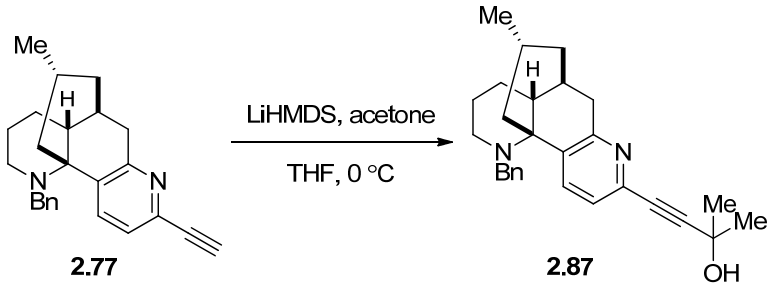
2.82: $[\alpha]^{23.0}_{D}$ +37.5° (*c* 0.40, CH_2Cl_2); R_f = 0.72 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.74 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 1H), 1.15 (s, 17H), 1.18-1.33 (m, 7H), 1.43-1.49 (m, 1H), 1.52-1.61 (m, 2H), 1.72-1.79 (m, 2H), 1.91 (dt, *J* = 3.6 and 12.4 Hz, 1H), 2.09-2.12 (m, 1H), 2.39-2.53 (m, 2H), 2.71 (d, *J* = 18.8 Hz, 1H), 2.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.04 (d, *J* = 15.0 Hz, 1H), 4.22 (d, *J* = 15.0 Hz, 1H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.33-7.37 (m, 3H), 7.45 (d, *J* = 6.8 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.3, 18.7, 20.9, 22.3, 26.5, 27.1, 34.0, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 60.4, 90.4, 106.6, 126.3, 126.5, 128.0, 128.2, 134.4, 138.3, 140.3, 142.2, 159.0; **IR**: *v* 2918, 1384 cm^{-1}; **HRMS** calcd. for $C_{34}H_{49}N_2Si^+$ [M +H^+]: 513.36595. Found: 513.36587.



2.77 **2.86**

To a solution of **2.77** (10 mg, 28 μmol, 1.0 equiv.) in THF (1 mL) at 0 °C was added LiHMDS solution (0.15 mL, 1.0 M in THF/toluene, 150 μmol, 5.4 equiv.) and neat ethyl chloroformate (20 μL, 0.26 mmol, 9.2 equiv.). After 2 hours the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 2/1 hexanes/EtOAc) to afford **2.86** (8.8 mg, 76%) as clear oil.

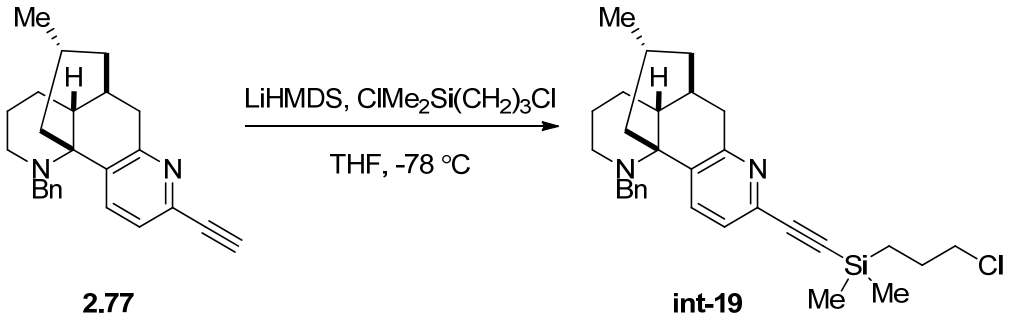
2.86: $[\alpha]^{23.0}_{D}$ +12.0° (*c* 0.25, CH_2Cl_2); R_f = 0.68 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.76 (d, *J* = 6.0 Hz, 3H), 0.88-0.94 (m, 1H), 1.14-1.36 (m, 5H), 1.40-1.52 (m, 2H), 1.55-1.61 (m, 1H), 1.74-1.80 (m, 2H), 1.92-1.96 (m, 1H), 2.11-2.14 (m, 1H), 2.36-2.42 (m, 1H), 2.51-2.55 (m, 1H), 2.72 (m, d, *J* = 18.8 Hz, 1H), 3.20 (dd, *J* = 6.8 and 18.8 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 4.12 (dd, *J* = 14.0 and 80.0 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 7.23-7.27 (m, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0, 20.8, 22.3, 26.5, 27.1, 33.8, 35.3, 38.1, 43.6, 45.9, 48.2, 50.8, 60.6, 62.2, 78.5, 84.7, 126.6, 126.7, 128.0, 128.3, 134.8, 137.2, 140.7, 142.0, 153.7, 160.1; **IR**: *v* 2923, 1710, 1219 cm^{-1}; **HRMS** calcd. for $C_{28}H_{33}N_2O_2^+$ [M +H^+]: 429.2542. Found: 429.2543.



2.77 **2.87**

To a solution of **2.94** (10 mg, 28 μmol, 1.0 equiv.) in THF (1 mL) at 0 °C was added LiHMDS solution (0.15 mL, 1.0 M in THF/toluene, 0.15 mmol, 5.4 equiv.) and after 20 minutes neat acetone (20 μL, 0.27 mmol, 9.7 equiv.) was added. After 10 minutes the reaction was diluted with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 →2/1 hexanes/EtOAc) to afford **2.129** (7.9 mg, 68%) as clear oil.

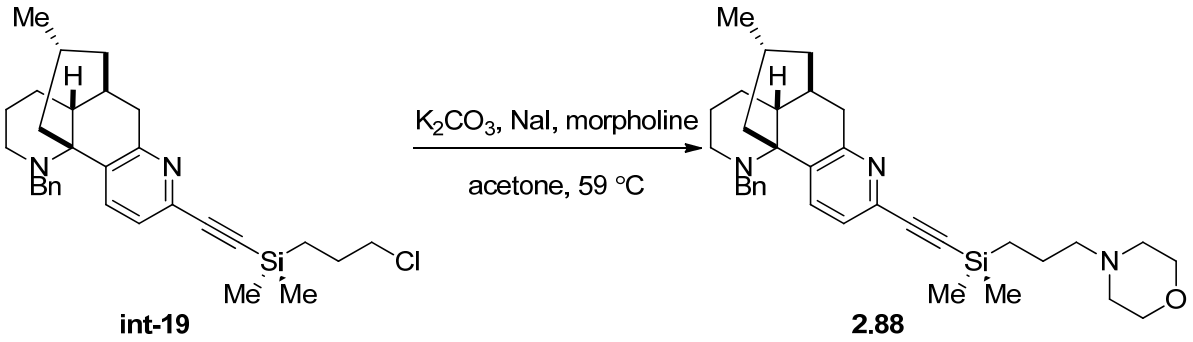
2.129: $[\alpha]^{23.0}_{D}$ +41.0° (*c* 0.56, CH_2Cl_2); R_f = 0.30 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.74 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 2H), 1.12-1.31 (m, 4H), 1.37-1.49 (m, 1H), 1.52-1.66 (m, 6H), 1.72-1.79 (m, 3H), 1.91 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.10-2.11 (m, 1H), 2.21-2.23 (m, 1H), 2.36-2.52 (m, 2H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.03 (d, *J* =14.0 Hz, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 7.25-7.30 (m, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.8, 22.3, 26.5, 27.0, 31.2, 33.9, 35.3, 38.1, 43.6, 45.7, 48.1, 50.7, 60.4, 65.5, 81.9, 92.8, 125.3, 126.5, 128.0, 128.2, 134.7, 138.4, 139.6, 142.1, 159.1; **IR**: *v* 3500, 1459 cm^{-1}; **HRMS** calcd. for $C_{28}H_{35}N_2O^+$ [M +H^+]: 415.2749. Found: 415.2749.



2.77 **int-19**

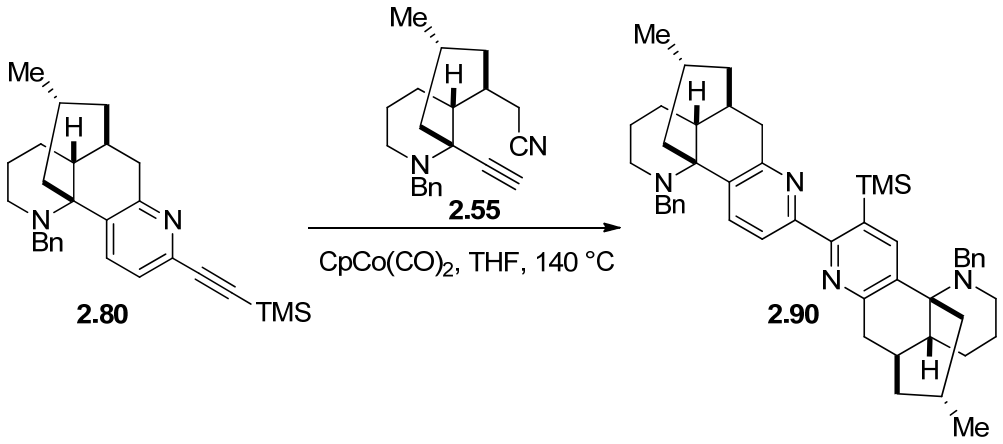
To a solution of **2.77** (21.0 mg, 41 μmol, 1.0 equiv.) in THF (1.5 mL) at –78 °C was added LiHMDS solution (77 μL, 1.0 M in THF/toluene, 77 μmol, 1.3 equiv.) and silyl chloride **X** (13 μL, 77 μmol, 1.3 equiv.). After 30 minutes the reaction was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (1/0 → 10/1 hexanes/EtOAc) to afford **int-19** (19.0 mg, 66%) as clear oil.

Int-19: $[\alpha]^{23.0}_D$ +41.0° (*c* 0.56, CH_2Cl_2); R_f = 0.30 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (s, 6H), 0.74 (d, *J* = 6.0 Hz, 3H), 0.82 (dt, *J* = 4.4 and 8.0 Hz, 2H), 1.11-1.32 (m, 4H), 1.43-1.63(m, 4H), 1.72-1.80 (m, 2H), 1.89-1.97 (m, 3H), 2.09-2.13 (m, 1H), 2.40 (dt, *J* = 1.2 and 13.2 Hz, 1H), 2.48-2.53 (m, 1H), 3.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 2H), 4.03 (d, *J* = 14.4 Hz, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 7.24-7.27 (m, 1H), 7.32-7.37 (m, 3H), 7.45 (dd, *J* = 0.8 and 8.0 Hz, 2H), 8.09 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.9, 13.7, 20.8, 22.3, 26.4, 27.0, 27.5, 33.9, 35.4, 38.1, 43.6, 45.7, 47.7, 48.1, 50.7, 60.5, 91.8, 105.2, 125.7, 126.5, 128.0, 128.2, 134.5, 138.7, 139.7, 142.1, 159.2; **IR**: *v* 2920, 1558 cm^{-1}; **HRMS** calcd. for $C_{30}H_{40}N_2SiCl^+$ [M +H^+]: 491.2649. Found: 491.2645.



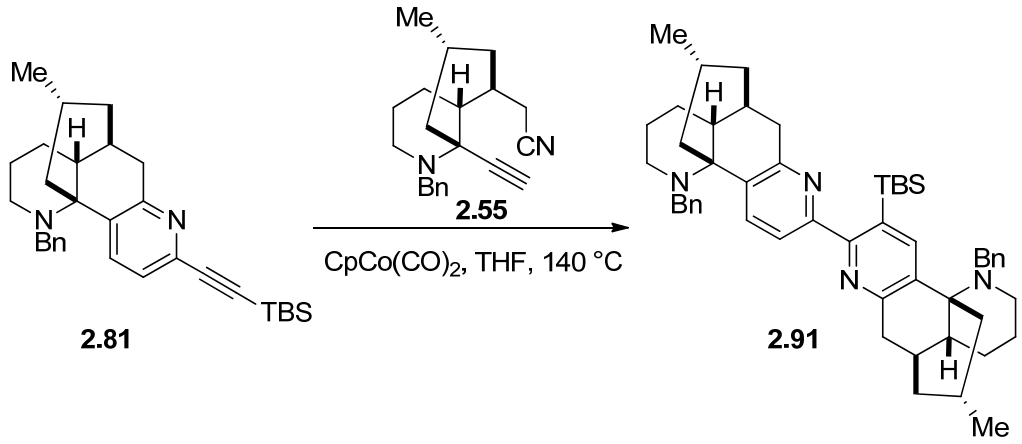
Pyridine **int-19** (15.0 mg, 31 μmol, 1.0 equiv.**)** was dissolved in acetone (1 mL) and NaI (15 mg, 3.3 mmol, 3.3 equiv.), morpholine (13 mL, 0.15 mmol, 5.0 equiv.), and K_2CO_3 (10 mg, 2.4 mmol, 2.4 equiv.) were added. The heterogeneous reaction was heated to reflux. After 48 hours the reaction was cooled to 23 °C, diluted with saturated NH_4Cl solution (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 hexanes/EtOAc → 10/1 CH_2Cl_2/MeOH) to afford **2.88** (13.8 mg, 83%) as pale yellow oil.

2.88: $[\alpha]^{23.0}_{D}$ +24.4° (*c* 0.86, CH_2Cl_2); R_f = 0.35 (silica gel, CH_2Cl_2/MeOH = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.24 (s, 6H), 0.67-0.70 (m, 2H), 0.74 (d, *J* = 6.4 Hz, 3H), 0.83-0.97 (m, 1H), 1.11-1.33 (m, 4H), 1.42-1.49 (m, 2H), 1.51-1.68 (m, 3H), 1.72-1.82 (m, 2H), 1.91 (dt, *J* = 3.6 and 12.8 Hz, 2H), 2.09-2.11 (m, 1H), 2.37-2.40 (m, 2H), 2.43-2.59 (m, 4H), 2.70 (d, *J* = 18.8 Hz, 1H), 3.18 (dd, *J* = 7.2 and 15.6 Hz, 1H), 3.72 (t, *J* = 4.8 Hz, 4H), 4.03 (d, *J* = 15.6 Hz, 1H), 4.21 (d, J = 15.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.9, 13.6, 20.80, 20.83, 22.3, 26.5, 27.1, 33.9, 35.3, 38.2, 43.7, 45.8, 48.1, 50.8, 53.7, 60.5, 62.1, 66.9, 92.5, 104.9, 125.6, 126.5, 128.0, 128.2, 134.5, 138.6, 139.8, 142.1, 159.2; **IR**: *v* 2925, 1450 cm^{-1}; **HRMS** calcd. for $C_{34}H_{48}N_3OSi^+$ [M +H^+]: 542.35666. Found: 542.35636.



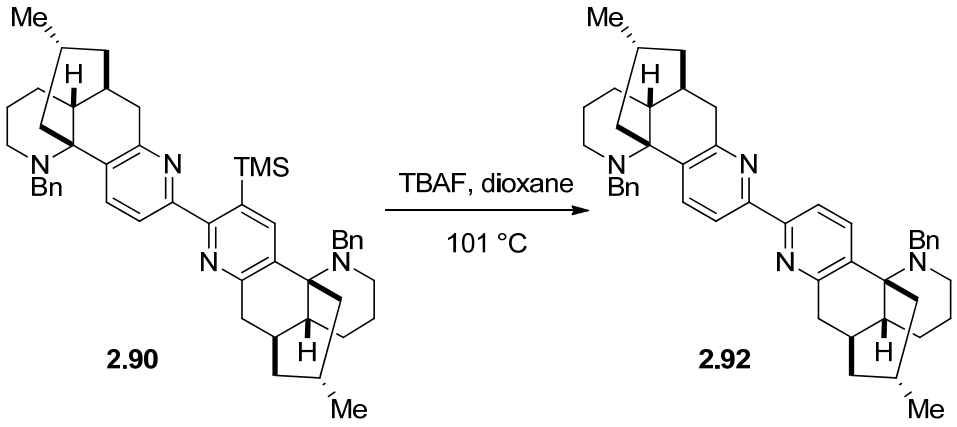
In a pressure tube **2.80** (18.5 mg, 43 μmol, 1.0 equiv.) and alkyne-nitrile **2.55** (20.0 mg, 65 μmol, 1.5 equiv.) were dissolved in degassed THF (4 mL). Neat $CpCo(CO)_2$ (30 μL, 34 μmol, 0.8 equiv.) was added and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 14 hours the mixture was cooled and the reaction was concentrated. The product was purified by silica gel chromatography (20/1 to 10/1 hexanes/EtOAc) to afford bipyridyl **2.90** (13.6 mg, 43%) as yellow oil.

2.90: $[\alpha]^{24}_{D}$ +26.3° (*c* 0.49, CH_2Cl_2); R_f = 0.65 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.20 (s, 9H), 0.74 (d, *J* = 6.4 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H), 1.10-1.59 (m, 14H), 1.70-1.83 (m, 4H), 1.90-1.96 (m, 2H), 2.13 (bs, 2H), 2.54 (brs, 4H), 2.73-2.78 (m, 2H), 3.19-3.28 (m, 2H), 4.11-4.27 (m, 4H), 7.23-7.27 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 4H), 7.51 (t, *J* = 8.0 Hz, 5H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.43 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 1.0, 21.4, 21.8, 22.3, 22.4, 26.3, 26.5, 27.1, 27.2, 34.1, 34.2, 35.1, 35.3, 38.8, 39.5, 43.9, 43.9, 45.9, 45.9, 48.1, 48.1, 51.0, 51.2, 60.3, 60.4, 121.0, 126.4, 126.4, 127.8, 128.0, 128.2, 128.2, 130.5, 135.2, 135.9, 137.3, 142.3, 142.5, 142.8, 156.9, 157.0, 158.0, 159.9; **IR**: *v* 1453, 1242, 838, 733 cm^{-1}; **HRMS** calcd. for $C_{49}H_{63}N_4Si^+$ [M $+H^+$]: 735.48220. Found: 735.48176.



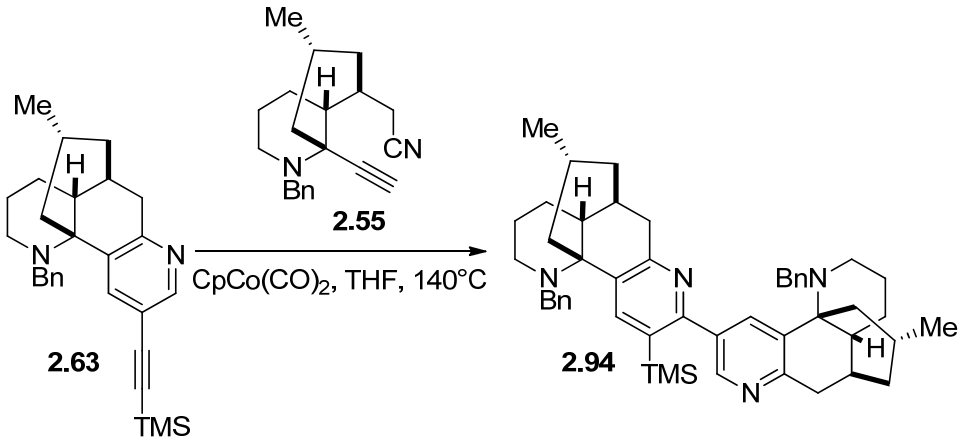
In a pressure tube alkyne nitrile **2.81** (15 mg, 32 μmol, 1.0 equiv.) and **2.55** (15 mg, 49 μmol, 1.5 equiv.) were dissolved in degassed THF (2 mL). Neat $CpCo(CO)_2$ (5.0 μL, 41 μmol, 1.3 equiv.) was added and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 10 hours the reaction was cooled and concentrated. The crude was purified by silica gel chromatography (20/1 → 10/1 hexanes/EtOAc) to afford **2.91** (7.2 mg, 29%) as yellow oil.

2.91: $[\alpha]^{23.0}_{D}$ +26.3° (*c* 0.38, CH_2Cl_2); R_f = 0.62 (silica gel, hexanes/EtOAc = 10/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ -0.11 (s, 3H), -0.10 (s, 3H), 0.76 (d, *J* = 6.0 Hz, 3H), 0.76 (d, *J* = 6.0 Hz, 3H), 0.83-1.02 (m, 12H), 1.15-1.19 (m, 2H), 1.26-1.43 (m, 5H), 1.47-1.63 (m, 4H), 1.70-1.84 (m, 3H), 1.90-1.95 (m, 2H), 2.11-2.14 (m, 2H), 2.51-2.55 (m, 4H), 2.72 (dd, *J* = 3.6 and 19.2 Hz, 2H), 3.22 (dd, *J* = 7.2 and 19.2 Hz, 2H), 4..8-4.14 (m, 2H), 4.23-4.29(m, 2H), 7.23-7.27 (m, 2H), 7.33-7.40 (m, 5H), 7.49-7.51 (m, 4H), 8.14 (d, *J* = 8.0 Hz, 2H), 8.45 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.0, -3.8, 14.1, 17.8, 21.3, 22.3, 22.4, 22.6, 26.38, 26.44, 27.1, 27.4, 34.1, 34.2, 34.7, 35.3, 38.7, 38.8, 43.8, 43.9, 45.6, 46.0, 48.1, 48.3, 50.95, 51.01, 60.2, 60.4, 121.9, 126.4, 126.4, 127.8, 128.0, 128.1, 128.2, 128.2, 134.6, 135.4, 137.1, 142.4, 142.7, 143.1, 157.0, 157.6, 158.1, 161.3; **IR**: *v* 2925, 2854, 733 cm^{-1}; **HRMS** calcd. for $C_{52}H_{69}N_4Si^+$ [M +H^+]: 777.52915. Found: 777.52834.



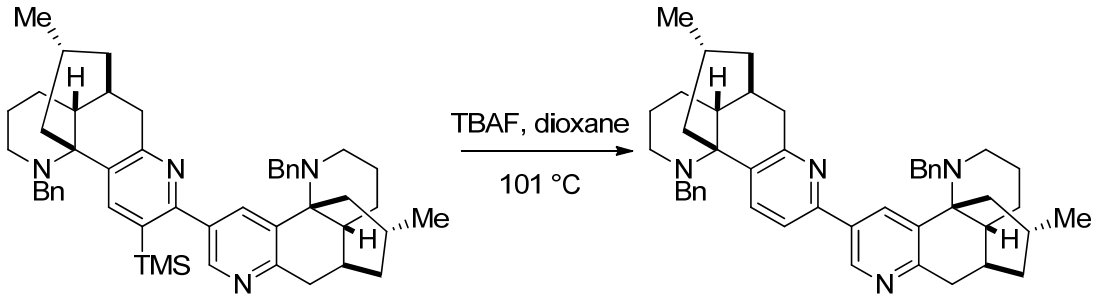
To a solution of **2.90** (21 mg, 29 μmol, 1.0 equiv.) in dioxane (1.5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 75 μmol, 5.2 equiv.). The resulting solution was placed in a heated oil bath. After 10 hours the reaction was concentrated and purified by silica gel chromatography (1/0 → 10/1 hexanes/EtOAc) to afford compound **2.92** (15.5 mg, 82%) as light yellow foam.

2.92: $\mathbf{R}_f$ = 0.65 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.74 (d, J = 6.5 Hz, 6H), 0.86-1.03 (m, 2H), 1.14-1.61 (m, 8H), 1.77-1.80 (m, 4H), 1.94 (dt, J = 4.5 and 11.5 Hz, 2H), 2.14 (brs, 2H), 2.52 (d, J = 9.5 Hz, 4H), 2.80 (d, J = 23.5 Hz, 2H), 3.29 (dd, J = 9.5 and 23.5 Hz, 2H), 4.12 (d, J = 18.0 Hz, 2H), 4.25 (d, J = 18.0 Hz, 2H), 7.23-7.27 (m, 6H), 7.36 (t, J = 9.5 Hz, 4H), 7.50 (d, J = 9.5 Hz, 4H), 8.10 (d, J = 10.0 Hz, 2H), 8.21 (d, J = 10.0 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.4, 26.5, 27.2, 29.7, 34.2, 35.6, 38.8, 34.8, 45.8, 48.2, 51.0, 60.5, 119.2, 126.5, 128.0, 128.2, 135.3, 138.0, 142.5, 154.1, 158.2; **IR**: ν 2965, 1601 cm^{-1}; **HRMS** calcd. for $C_{46}H_{55}N_4Si^+$ [M +H^+]: 663.44267. Found: 663.44200.



In a pressure tube **2.63** (14 mg, 33 µmol, 1.0 equiv.) and alkyne-nitrile **2.55** (14 mg, 46 µmol, 1.4 equiv.) were dissolved in degassed THF (2 mL). Neat CpCo(CO)2 (5 µL, 41 µmol, 1.2 equiv.) was added and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C. After 10 hours the mixture was cooled to 23 °C and the reaction was concentrated. The crude was purified by silica gel chromatography (20/1 →10/1 hexanes/EtOAc) to afford bipyridyl **2.94** (6.8 mg, 28%) as yellow oil.

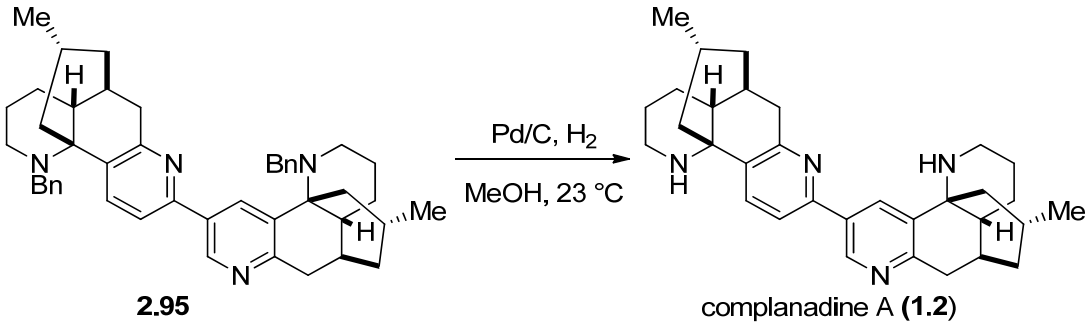
2.94:[α]$^{23.0}_{D}$ +34.2° (*c* 0.30, CH_2Cl_2); R_f = 0.2 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.10 (s, 9H), 0.79 (d, *J* = 5.6 Hz, 3H), 0.82 (d, *J* = 6.0 Hz, 3H), 0.85-0.91 (m, 2H), 1.12-1.43 (m, 7H), 1.49-1.66 (m, 6H), 1.75-1.84 (m, 4H), 1.93-2.00 (m, 2H), 2.12-2.18 (m, 2H), 2.45-2.63 (m, 3H), 2.76 (dd, *J* = 3.6 and 18.4 Hz, 2H), 3.23 (dt, *J* = 7.6 and 19.0 Hz, 2H), 4.04-4.29 (m, 4H), 7.22-7.42 (m, 6H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.38 (s, 1H), 8.48 (d, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.6, 14.1, 20.7, 21.7, 22.3, 22.6, 24.9, 26.3, 26.6, 27.1, 31.8, 34.0, 34.1, 35.3, 38.3, 39.4, 43.8, 45.4, 45.8, 47.8, 48.0, 50.7, 51.2, 60.2, 60.6, 126.4, 126.5, 127.6, 127.8, 128.1, 128.2, 128.4, 130.8, 134.3, 135.4, 136.9, 137.5, 141.9, 142.0, 142.7, 147.0, 157.9, 158.5, 159.5; **IR**: *v* 3390, 2922, 1559, 732 cm^{-1}; **HRMS** calcd. for $C_{49}H_{63}N_4Si^+$ [M +H^+]: 735.4822. Found: 735.4820.



2.94 **2.95**

To a solution of **2.94** (8.1 mg, 11 μmol, 1.0 equiv.) in dioxane (1 mL) at 23 °C was added TBAF solution (1.0 M in THF, 50 μL, 50 μmol, 4.6 equiv.) and the reaction was placed in a heated oil bath. After 10 hours the mixture was cooled to 23 °C, diluted with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 1/1 hexanes/EtOAc) to afford **2.95** (7.3 mg, 99%) as light yellow oil.

2.94:$[\alpha]^{23.0}_{D}$ +36.9° (*c* 0.73, CH_2Cl_2); $\mathbf{R}_f$ = 0.40 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.76 (d, *J* = 6.0 Hz, 3H), 0.77 (d, *J* = 6.0 Hz, 3H), 1.17-1.21 (m, 2H), 1.23-1.37 (m, 3H), 1.37-1.44 (m, 1H), 1.44-1.55 (m, 2H), 1.55-1.69 (m, 4H), 1.73-1.83 (m, 4H), 1.92-1.99 (m, 2H), 2.13-2.19 (m, 2H), 2.53-2.57 (m, 4H), 2.79 (dd, *J* = 18.8 and 34.4 Hz, 2H), 3.22-3.35 (m, 2H), 4.10-4.32 (m, 4H), 7.24-7.28 (m, 4H), 7.38 (dt, *J* = 3.6 and 7.2 Hz, 4H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz. 1H), 8.74 (d, *J* = 2.4 Hz, 1H), 8.98 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 21.7, 22.3, 22.4, 26.4, 26.6, 27.2, 34.1, 34.2, 35.3, 35.6, 38.7, 39.3, 43.8, 45.9, 46.0,48.0, 48.2, 50.9, 51.2, 60.4, 60.5, 118.4, 126.4, 126.5, 128.0, 128.2, 132.7, 133.3, 135.3, 137.1, 137.9, 142.4, 142.6, 145.3, 152.5, 158.7, 158.9; **IR**: *v* 3446, 2921, 1447, 732 cm^{-1}; **HRMS** calcd. for $C_{46}H_{55}N_4^+$ [M +H^+]: 663.4427. Found: 663.4427.

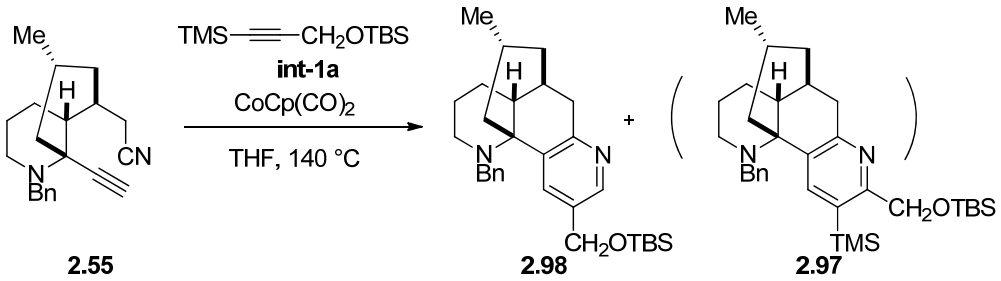


2.95 complanadine A (**1.2**)

To **2.95** (8.0 mg, 12 μmol, 1.0 equiv.) in THF (1 mL) solid 10% palladium on carbon (2.0 mg, 15.6 μmol, 0.16 equiv.) was added then the heterogeneous solution was rapidly stirred under H_2 (1 atm) at 23 °C. After 20 hours the solution was filtered through a celite pad and concentrated to afford the complanadine A (**1.2**) (5.1 mg, 88%) as pale yellow oil.

Additional purification was achieved as follows: from above complanadine A (12 mg, 25 μmol, 1.0 equiv.) was dissolved in 5% HCl solution (5 mL) and washed with Et_2O (2 × 5 mL), the aqueous layer was adjusted to a pH of 13 with 10% aqueous NaOH solution, and the white suspension was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to provide complanadine A (**1.2**) (5.1 mg, 88%) as pale yellow oil.

Complanadine A (**1.2**)**:** $[\alpha]^{24}_D$ +14.5° (*c* 0.30, MeOH); **^{1}H NMR** (400 MHz, MeOH): δ 0.85 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 1.21-1.49 (m, 10H), 1.53-1.64 (m, 5H), 1.68-1.72 (m, 1H), 1.75-1.81 (m, 2H), 1.85-1.89 (m, 2H), 2.18-2.22 (m, 2H), 2.48-2.57 (m, 2H), 2.76-2.85 (m, 4H), 3.20-3.30 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.93 (s, 1H); **^{13}C NMR** (100 MHz, MeOH): δ 22.4, 27.1, 27.3, 27.7, 34.8, 34.9, 35.7, 36.2, 42.1, 44.7, 44.8, 44.9, 51.6, 51.7, 57.8, 57.9, 120.4, 133.7, 135.0, 135.9, 136.6, 137.6, 146.1, 153.7, 159.9, 160.5; **IR**: ν 2913, 1575, 1436 cm^{-1}; **HRMS** calcd. for $C_{32}H_{43}N_4^+$ [M+H$^+$]: 483.34877. Found: 483.34828.

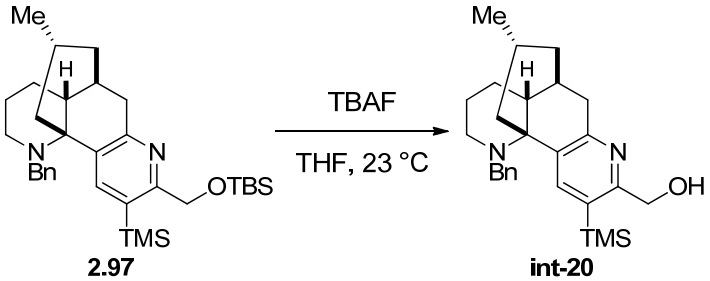


2.55 **2.98** **2.97**

In a pressure tube alkyne **int-1a** (218 mg, 0.90 mmol, 2.5 equiv.) and alkyne-nitrile **2.55** (110 mg, 0.36 mmol, 1.0 equiv.) were dissolved in freshly degassed THF (2.0 mL). Neat $CpCo(CO)_2$ (60 μL, 0.48 mmol, 1.4 equiv.) was added and the tube was sealed. The resulting solution was placed in an 140 °C oil bath. After 30 hours the reaction was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (1/0 → 5/1 hexanes/EtOAc) to afford **2.98** (65 mg, 34%) as a brown oil and unreacted **2.55** (14 mg, 11%) was recovered.

If the reaction was run at 0.05 M, the ratio is 1/3 (**2.98**/**2.97**). The undesired product **2.97** was subjected to desiylation for characterization.

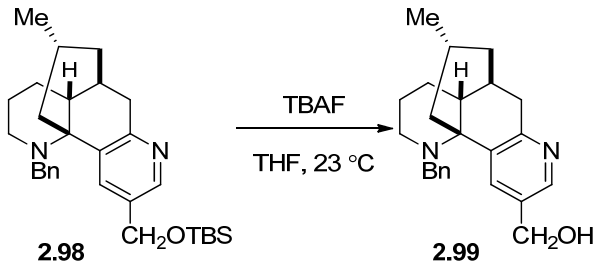
2.98: $[\alpha]^{23.0}_{D}$ +28.5° (*c* 0.23, CH_2Cl_2); R_f = 0.41 (silica gel, hexanes/EtOAc = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.13 (d, *J* = 2.0 Hz, 6H), 0.75 (d, *J* = 6.0 Hz, 3H), 0.95 (s, 9H), 1.11-1.35 (m, 4H), 1.43-1.58 (m, 3H), 1.71-1.80 (m, 2H), 1.93 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.09-2.12 (m, 1H), 2.43-2.52 (m, 2H), 3.19 (dd, *J* = 7.2 and 18.8 Hz, 1H), 4.14 (d, *J* = 14.4 Hz, 1H), 4.23 (d, *J* = 14.4 Hz, 1H), 4.77 (s, 2H), 7.22-7.26 (m, 1H), 7.32-7.36 (m, 2H), 7.47-7.49 (m, 2H), 8.10 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -5.2, -5.1, 18.4, 21.3, 22.4, 25.9, 26.4, 27.1, 34.0, 35.1, 38.7, 43.8, 45.8, 48.1, 51.1, 60.4, 63.0, 126.4, 127.9, 128.2, 132.5, 134.4, 137.7, 142.4, 144.9, 157.3; **IR**: *v* 2918, 1653, 1094 cm^{-1}; **HRMS** calcd. for $C_{30}H_{45}N_2OSi^+$ [M +H^+]: 477.33012. Found: 477.32948.



2.97 **int-20**

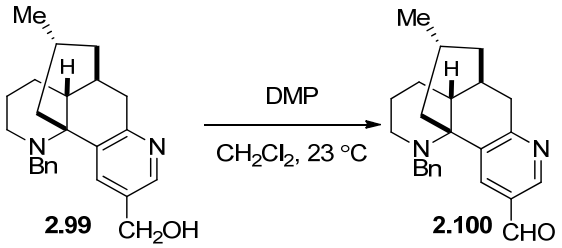
To a solution of **2.97** (61 mg, 0.13 mmol, 1.0 equiv.) in THF (5 mL) at 23 °C was added TBAF solution (0.15 mL, 1.0 M in THF, 0.15 mmol, 1.2 equiv.). After 30 minutes the mixture was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (10/1 → 1/1 hexanes/EtOAc) to afford **int-20** (12 mg, 22%) as light brown foam.

Int-20:$[\alpha]^{23.0}_D$ +57.1° (*c* 0.35, CH_2Cl_2); $\mathbf{R}_f$ = 0.35 (silica gel, Hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.35 (s, 9H), 0.76 (d, *J* = 6.0 Hz, 3H), 1.14-1.34 (m, 5H), 1.43-1.57 (m, 3H), 1.71-1.80 (m, 2H), 1.89 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.10-2.12 (m, 1H), 2.40-2.53 (m, 2H), 2.65 (d, *J* = 19.2 Hz, 1H), 3.16 (dd, *J* = 7.2 and 19.2 Hz, 1H), 4.09 (d, *J* = 14.0 Hz, 1H), 4.22 (d, *J* = 14.0 Hz, 1H),4.73 (d, *J* = 1.6 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 8.26 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.0, 22.0, 23.0, 27.0, 27.6, 34.6, 35.5, 39.6, 44.3, 46.6, 48.6, 51.6, 60.6, 64.1, 127.0, 128.4, 128.8, 136.2, 142.1, 143.2, 157.5, 159.4, 163.5; **IR**: *v* 2923, 1068, 839 cm^{-1}; **HRMS** calcd. for $C_{27}H_{39}N_2OSi^+$ [M +H^+]: 435.2832. Found: 435.2826.



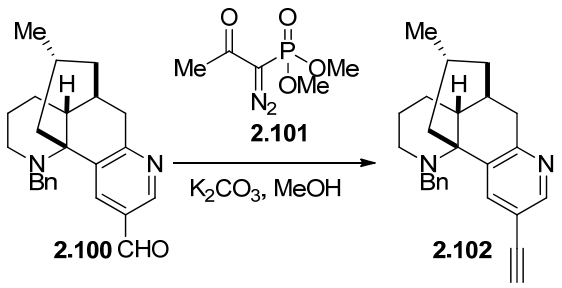
To a solution of **2.98** (200 mg, 0.42 mmol, 1.0 equiv.) in THF (5 mL) at 23 °C was added TBAF solution (0.80 mL, 1.0 M in THF, 0.80 mmol, 1.9 equiv.). After 30 minutes the reaction was concentrated. The crude material was purified by silica gel chromatography (5/1 → 0/1 hexanes/EtOAc) to afford **2.99** (119 mg, 78%) as light brown oil.

2.99: $[\alpha]^{23.0}_{D}$ +29.0° (*c* 0.24, CH_2Cl_2); R_f = 0.32 (silica gel, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.75 (d, *J* = 6.0 Hz, 3H), 0.91-0.99 (m, 1H), 1.12-1.33 (m, 4H), 1.45-1.58 (m, 3H), 1.74-1.80 (m, 2H), 1.92 (dt, *J* = 4.0 and 13.2 Hz, 1H), 2.08-2.12 (m, 1H), 2.39-2.53 (m, 2H), 2.69 (d, *J* = 18.8 Hz, 1H), 3.18 (dd, *J* = 6.8 and 18.8 Hz, 1H), 4.09 (d, *J* = 14.4, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 4.73 (s, 2H), 7.23-7.26 (m, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 8.11 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 22.4, 26.4, 27.0, 33.9, 35.0, 38.5, 43.7, 45.8, 48.1, 51.0, 60.4, 63.1, 126.5, 128.0, 128.2, 133.6, 134.1, 138.1, 142.2, 145.7, 157.9; **IR**: *v*, 2921, 1453, 732 cm^{-1}; **HRMS** calcd. for $C_{24}H_{31}N_2O^+$ [M +H^+]: 363.2436. Found: 363.2433.



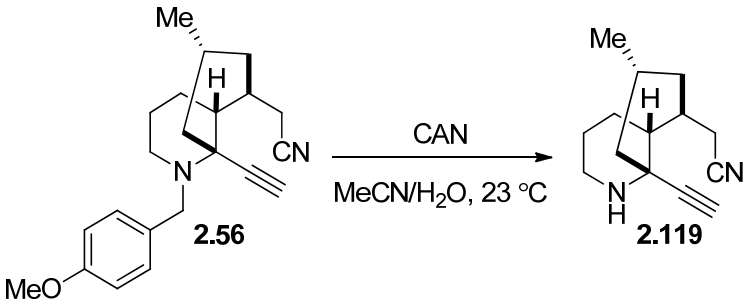
To a solution of **2.99** (46 mg, 0.13 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added solid Dess-Martin periodiane (215 mg, 0.51 mmol, 4.0 equiv.) at 23 °C. After 30 minutes the heterogeneous solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 2/1 Hexanes/EtOAc) to afford **2.100** (44.1 mg, 96%) as pale yellow oil.

2.100: $[\alpha]^{23.0}_D$ +28.5° (*c* 0.23, CH_2Cl_2); R_f = 0.20 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.77 (d, *J* = 6.0 Hz, 3H), 1.14-1.37 (m, 4H), 1.53-1.63 (m, 3H), 1.75-1.81 (m, 2H), 1.99 (dt, *J* = 3.2 and 12.4 Hz, 1H), 2.11-2.18 (m, 1H), 2.35-2.42 (m, 1H), 2.53-2.58 (m, 1H), 2.79 (d, *J* = 19.6 Hz, 1H), 3.27 (dd, *J* = 7.2 and 19.2 Hz, 1H), 4.18 (dd, *J* = 14.4 and 64.0 Hz, 2H), 7.24-7.28 (m, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 8.57 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 10.1 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 22.3, 26.4, 27.1, 33.8, 36.0, 38.2, 43.5, 45.8, 48.1, 51.0, 60.5, 126.7, 128.0, 128.3, 130.3, 134.9, 139.3, 141.8, 149.0, 165.5, 191.3; **IR**: *v* 2919, 1698, 1384 cm^{-1}; **HRMS** calcd. for $C_{24}H_{29}N_2O^+$ [M +H^+]: 361.2280. Found: 361.2278.



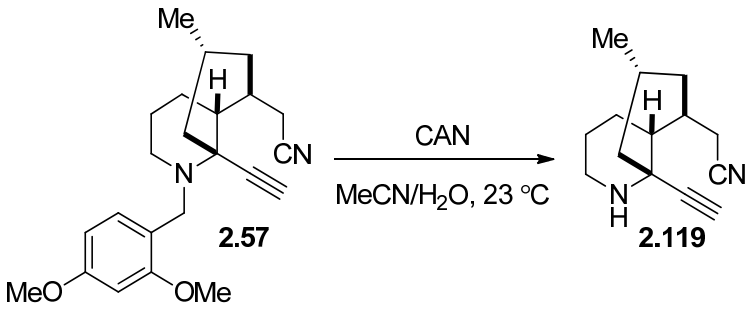
To a solution of **2.100** (50 mg, 0.14 mmol, 1.0 equiv.) and K_2CO_3 (47.9 mg, 0.35 mmol, 2.5 equiv.) in methanol (2 mL) was added dimethyl-1-diazo-2-oxopropylphosphate **2.101** (66.6 mg, 0.35 mmol, 2.5 equiv.) at 0 °C. After 8 hours the reaction was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 5/1 hexanes/EtOAc) to afford **2.102** (42.3 mg, 86%) as white foam.

2.102: $[\alpha]^{23.0}_{D}$ +27.5° (*c* 0.29, CH_2Cl_2); R_f = 0.65 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.76 (d, *J* = 6.0 Hz, 3H), 1.14-1.33 (m, 4H), 1.48-1.50 (m, 1H), 1.56-1.64 (m, 2H), 1.73-1.83 (m, 2H), 1.93 (dt, *J* = 3.6 and 12.8 Hz, 1H), 2.10-2.13 (m, 1H), 2.40-2.54 (m, 2H), 2.68 (d, *J* = 19.2 Hz, 1H), 3.16-3.23 (m, 2H), 4.05 (d, *J* = 14.0 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 7.25-7.27 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9, 22.3, 26.4, 27.0, 33.8, 35.4, 38.2, 43.6, 45.7, 48.1, 50.8, 60.3, 79.2, 81.4, 116.7, 126.6, 128.0, 128.3, 137.5, 137.9, 142.0, 149.8, 158.9; **IR**: *v* 2921, 1450, 1384 cm^{-1}; **HRMS** calcd. for $C_{25}H_{29}N_2^+$ [M +H^+]: 357.2331. Found: 357.2326.



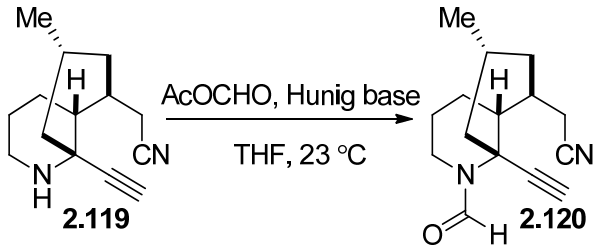
Amine **2.56** (600 mg, 1.78 mmol, 1.0 equiv.) was dissolved in acetonitrile/water (6/1, 15 mL). Solid CAN (4.0 g, 7.3 mmol, 4.1 equiv.) was added in one portion and the solution was placed in a 75 °C oil bath. After 5 hours the mixture was neutralized with aqueous NaOH solution (1.0 M, 15 mL) and filtered through a celite pad. The mixture was extracted with EtOAc (3 × 15 mL) and washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (the column was neutralized with 1% Et_3N in hexane) (5/1 → 0/1 hexanes/EtOAc) to afford the secondary amine **2.119** (260 mg, 67 %, m.p. 153.8-154.2 °C) as pale yellow solid.

2.119:$[\alpha]^{24}_D$ -24.1° (*c* 0.27, CH_2Cl_2); $\mathbf{R}_f$ = 0.25 (silica gel, neutralized by Et_3N, EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.95 (d, J = 6.4 Hz, 3H), 1.13 (t, J = 12.1 Hz, 1H), 1.24-1.32 (m, 1H), 1.43-1.66 (m, 4H), 1.70-1.80 (m, 2H), 1.91-2.08 (m, 3H), 2.44 (s, 1H), 2.50-2.56 (m, 1H), 2.81-2.86 (m, 1H), 2.93 (dd, J = 4.0 and 17.2 Hz, 1H), 3.04-3.11 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9, 21.8, 24.1, 26.1, 26.4, 36.3, 38.4, 42.3, 45.8, 48.6, 54.1, 75.1, 87.5, 120.5; **IR**: ν 3285, 1457, 1124, 637 cm^{-1}; **HRMS** calcd. for $C_{14}H_{21}N_2^+$ [M+H$^+$]: 217.17014. Found: 217.16996.



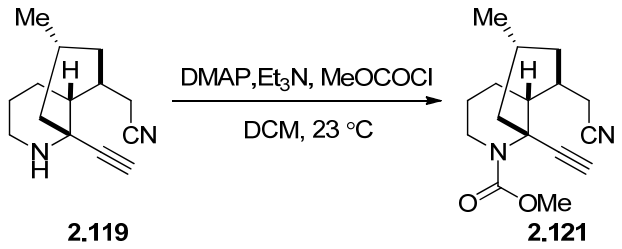
Amine **2.57** (200 mg, 0.55 mmol, 1.0 equiv) was dissolved in acetonitrile/water (6/1, 12 mL) at 23 °C. Solid CAN (500 mg, 0.91 mmol, 1.6 equiv.) was added in one portion. After 5 min at 23 °C the mixture was neutralized with aqueous NaOH solution (1M, 5 mL) and filtered through a celite pad. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (column was neutralized with 1% Et_3N in hexane) (5/1 → 0/1 hexanes/EtOAc) to afford the secondary amine **2.119** (81 mg, 70 %, m.p. 153.8- 154.2 °C) as pale yellow solid.

Spectral data the same as above.



To a solution of **2.119** (260 mg, 1.2 mmol, 1.0 equiv.) in THF (7 mL) was added neat AcOCHO (200 μL, 1.9 mmol, 1.6 equiv.) and Hünig's base (300 μL, 1.6 mmol, 1.4 equiv.) at 23 °C. After 30 minutes the solution was diluted with aqueous saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford **2.120** (290 mg, 97%, m.p. 155.0-155.2 °C) as pale yellow solid.

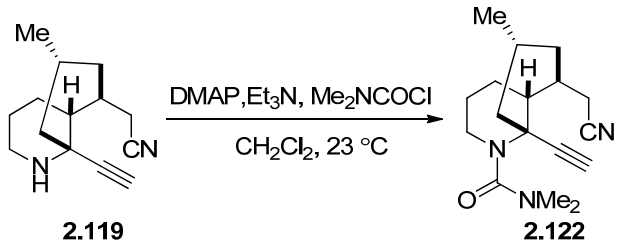
2.120: $[\alpha]^{24}_{D}$ +81.8° (*c* 1.0, CH_2Cl_2); R_f = 0.28 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.8 Hz, 3H), 1.32 (dt, J = 5.2 and 13.6 Hz, 1H), 1.42-1.67 (m, 4H), 1.78-1.85 (m, 2H), 1.98-2.19 (m, 3H), 2.34 (d, J = 11.6 Hz, 1H), 2.59-2.64 (m, 2H), 2.87-2.97 (m, 2H), 4.47-4.51 (m, 1H), 8.36 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.9, 21.9, 24.4, 25.1, 26.5, 36.5, 37.6, 37.7, 44.0, 46.9, 57.4, 76.6, 83.8, 119.8, 158.7; **IR**: 1659, 1385, 1131, 913 cm^{-1}; **HRMS** calcd. for $C_{15}H_{21}N_2O^+$ [M+H$^+$]: 245.16539. Found: 245.16486.



2.119 **2.121**

To a solution of **2.119** (50 mg, 0.23 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was added Et_3N (0.097 mL, 0.69 mmol, 3.0 equiv.) and methyl chloroformate (36 µL, 0.46 mmol, 2.0 equiv.) at 23 °C. After one hour the resulted solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel chromatography (10/1 → 5/1 hexanes/EtOAc) to afford carbamate **2.121** (55 mg, 87%) as yellow oil.

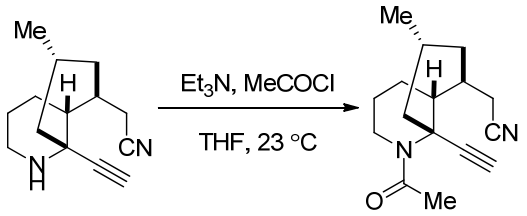
2.121: $[\alpha]^{23.0}_{D}$ +30.0° (*c* 0.20, CH_2Cl_2); R_f = 0.70 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.30 (dt, *J* = 5.2 and 13.2 Hz, 1H), 1.40 (t, *J* = 13.2 Hz, 1H), 1.51-1.63 (m, 2H), 1.70-1.80 (m, 3H), 1.91-1.99 (m, 2H), 2.14-2.19 (m, 1H), 2.51 (s, 1H), 2.63 (ddd, *J* = 0.8, 4.0 and 17.2 Hz, 1H), 2.94 (dd, *J* = 12.0 and 17.2 Hz, 1H), 3.24-3.31 (m, 2H), 3.64 (s, 3H), 3.91-3.96 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.2, 22.0, 24.7, 24.8, 25.9, 37.4, 37.9, 43.8, 45.6, 45.7, 52.3, 58.2, 75.3, 84.6, 120.3, 156.7; **IR**: *v* 2924, 1713, 1384, 1268 cm^{-1}; **HRMS** calcd. for $C_{16}H_{23}N_2O_2^+$ [M +H$^+$]: 275.1759. Found: 275.1753.



2.119 **2.122**

To a solution of secondary amine **2.119** (100 mg, 0.46 mmol, 1.0 equiv.) in THF (5 mL) solid DMAP (56 mg, 0.46 mmol, 1.0 equiv.) was added following by Et_3N (0.30 mL, 2.3 mmol, 5.0 equiv.) and neat dimethylcarbamoyl chloride (1.0 mL, 10.2 mmol, 22.0 equiv.) at 23 °C. After 12 minutes the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (5/1 → 1/1 hexanes/EtOAc) to afford urea **2.122** (96 mg, 72%) as yellow oil.

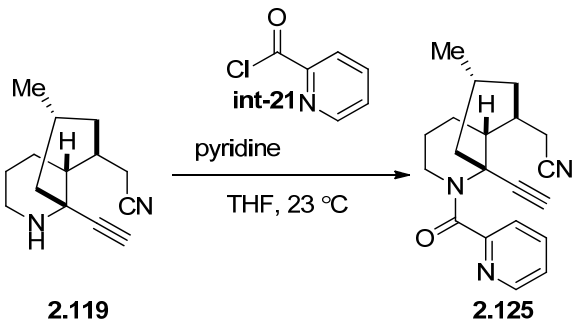
2.122: $[\alpha]^{23.0}_{D}$ +54.5° (*c* 0.11, CH_2Cl_2); R_f = 0.50 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.78 (t, *J* = 12.4 Hz, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 1.18-1.25 (m, 2H), 1.42-1.73 (m, 5H), 1.86-1.99 (m, 2H), 2.02-2.08 (m, 1H), 2.50 (s, 1H), 2.55 (ddd, *J* = 0.8, 4.0 and 17.2 Hz, 1H), 2.73 (td, *J* = 2.4 and 12.0 Hz, 1H), 2.84 (brs, 6H), 2.88-2.96 (m, 1H), 3.12 (td, *J* = 2.8 and 12.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3, 21.9, 24.1, 25.6, 26.4, 37.2, 38.4, 44.0, 46.5, 47.0, 56.3, 85.1, 120.5, 139.8, 163.3; **IR**: *v* 2924, 1652, 1385 cm^{-1}; **HRMS** calcd. for $C_{17}H_{26}N_3O^+$ [M +H$^+$]: 288.2076. Found: 288.2068.



2.119 **2.123**

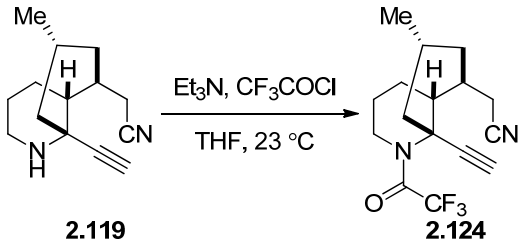
To a solution of **2.119** (200 mg, 0.93 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added neat acetyl chloride (0.20 mL, 0.28 mmol, 3.0 equiv.) and neat triethylamine (0.28 mL, 0.20 mmol, 2.0 equiv.) at 50 °C. After 2 h the resulted solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to amide **2.123** (178 mg, 78%) as yellow oil.

2.123: $[\alpha]^{23.0}_D$ +22.5° (*c* 0.80, CH_2Cl_2); R_f = 0.40 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.0 Hz, 3H), 1.24-1.33 (m, 2H), 1.52-1.59 (m, 1H), 1.63-1.71 (m, 1H), 1.76-1.97 (m, 5H), 2.08 (s, 3H), 2.14-2.20 (m, 1H), 2.50 (s, 1H), 2.65 (ddd, *J* = 1.2, 4.0 and 17.2 Hz, 1H), 2.95 (dd, *J* = 11.6 and 17.2 Hz, 1H), 3.34-3.42 (m, 2H), 3.52-3.58 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3, 21.8, 24.3, 24.6, 24.6, 25.6, 37.3, 38.0, 43.9, 44.4, 44.8, 58.1, 75.0, 84.5, 120.2, 172.1; **IR**: *v* 3216, 1650, 1390 cm^{-1}; **HRMS** calcd. for $C_{16}H_{23}N_2O^+$ [M $+H^+$]:259.1810. Found: 259.1807.



To a solution of **2.119** (15 mg, 69 μmol, 1.0 equiv.) in THF (3 mL) was added pyridine (17 μL, 0.21 mmol, 3.0 equiv.) and acid chloride **int-21** (19 μL, 0.14 mmol, 2.0 equiv.) and the solution was placed in a 50 °C oil bath. After 3 hours the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford amide **2.125** (11 mg, 49%) as yellow oil.

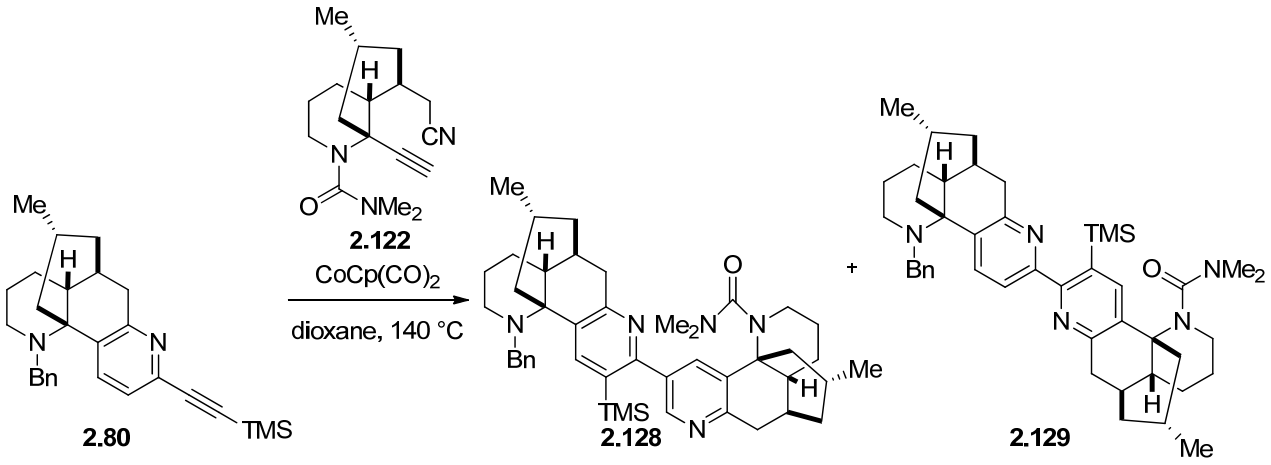
2.125: $[\alpha]^{23.0}_{D}$ -11.4° (*c* 0.35, CH_2Cl_2); R_f = 0.38 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.35 (dt, *J* = 5.2 and 13.2 Hz, 1H), 1.41 (t, *J* = 13.2 Hz, 1H), 1.59-1.63 (m, 1H), 1.70-1.87 (m, 3H), 1.94-2.09 (m, 3H), 2.20-2.24 (m, 1H), 2.59 (s, 1H), 2.69 (ddd, *J* = 0.8, 4.0 and 17.2 Hz, 1H), 2.99 (dd, *J* = 12.0 and 17.2 Hz, 1H), 3.22-3.29 (m, 1H), 3.50 (dt, *J* = 2.4 and 12.8 Hz, 1H), 3.61-3.66 (m, 1H), 7.34 (ddd, *J* = 1.2, 4.8 and 8.8 Hz, 1H), 7.69 (dt, *J* = 1.2 and 7.6 Hz, 1H), 7.79 (dt, *J* = 2.0 and 7.6 Hz, 1H), 8.59 (dq, *J* = 1.2, and 5.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3, 21.9, 24.6, 24.7, 25.7, 37.5, 38.0, 44.1, 45.2, 46.4, 58.2, 75.7, 84.2, 120.3, 124.1, 124.9, 137.2, 148.6, 155.0, 171.5; **IR**: *v* 2926, 1650, 1384 cm^{-1}; **HRMS** calcd. for $C_{20}H_{24}N_3O^+$ [M +H^+]: 322.1919. Found: 322.1915.



2.119 **2.124**

To a solution of **2.119** (50 mg, 0.23 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was added trifloroacetic anhydride (64 μL, 0.46 mmol, 2.0 equiv.) and triethylamine (0.097 mL, 0.69 mmol, 3.0 equiv.) at 23 °C. After 30 minutes the solution was diluted with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford amide **2.124** (23 mg, 32%) as white foam.

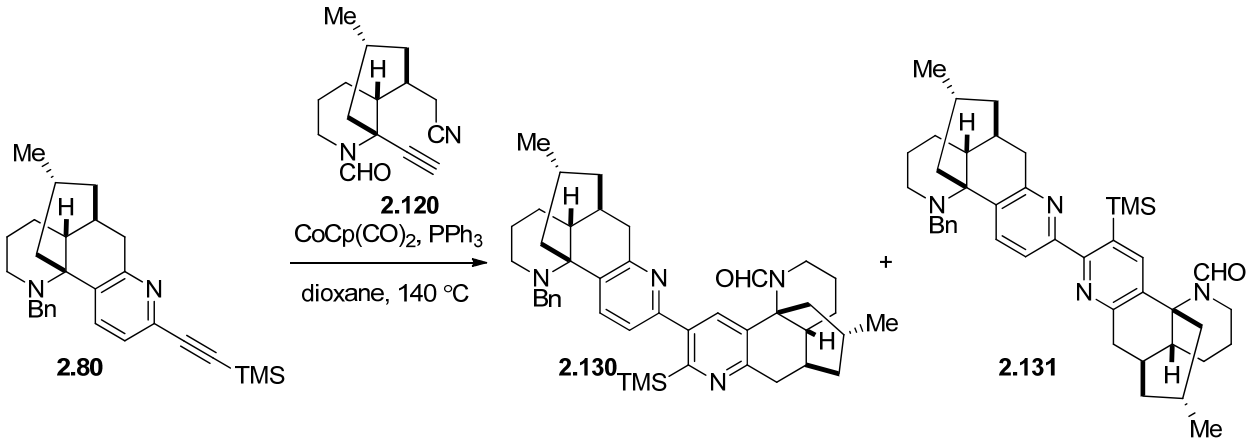
2.124: $[\alpha]^{23.0}_{D}$ +58.0° (*c* 0.50, CH_2Cl_2); R_f = 0.55 (silica gel, hexanes/EtOAc = 4/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.4 Hz, 3H), 1.28-1.42 (m, 2H), 1.58-1.66 (m, 1H), 1.69-1.77 (m, 1H), 1.81-2.00 (m, 5H), 2.18-2.24 (m, 1H), 2.61 (s, 1H), 2.67 (ddd, *J* = 1.2, 4.0 and 16.8 Hz, 1H), 2.92 (dd, *J* = 12.0 and 16.8 Hz, 1H), 3.25 (dt, *J* = 2.8 and 13.2 Hz, 1H), 3.47-3.54 (m, 1H), 3.65-3.71 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.2, 21.8, 24.0, 24.5, 24.7, 37.2, 37.8, 42.80, 42.84, 43.9, 44.4, 60.1, 82.8, 116.4 (t, *J* = 288.7 Hz), 119.9, 157.0 (t, *J* = 34.9 Hz); **IR**: *v* 3265, 2956, 1689, 1184 cm^{-1}; **HRMS** calcd. for $C_{16}H_{20}N_2OF_3^+$ [M +H^+]:313.1528. Found: 313.1523.



In a pressure tube alkyne-nitrile **2.122** (11 mg, 38 μmol, 1.4 equiv.) and pyridyl-alkyne **2.80** (12 mg, 28 μmol, 1.0 equiv.) were dissolved in degassed dioxane (2.5 mL). Neat $CpCo(CO)_2$ (5 μL, 41 μmol, 1.7 equiv.) and triphenylphosphine (44 mg, 0.17 mmol, 6.0 equiv.) were added and the tube was sealed. The resulting solution was placed in an oil bath heated to 140 °C for 24 hours. The mixture was cooled and the solvent was removed. The product was purified by silica gel chromatography (20/1 to 2/1 hexanes/EtOAc) to afford bipyridyl **2.128** (4.5 mg, 22%) and bipyridyl **2.129** (4.1 mg, 20%) both yellow oils.

2.128: $[\alpha]^{23.0}_{D}$ +62.2° (*c* 0.45, CH_2Cl_2); R_f = 0.50 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.74 (d, *J* = 5.6 Hz, 3H), 0.79 (d, *J* = 5.6 Hz, 3H), 1.15-1.61 (m, 11 H), 1.72-2.05 (m, 8 H), 2.12 (brs, 2H), 2.21-2.25 (m, 1H), 2.50-2.54 (m, 2H), 2.72-2.88 (m, 3H), 3.02 (s, 6H), 3.05-3.09 (m ,1H), 3.18-3.27 (m, 2H), 4.12 (d, *J* = 14.4 Hz, 1H), 4.24 (d, *J* = 14.4 Hz, 1H), 7.24-7.27 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 1.0, 14.7, 21.4, 22.2, 22.3, 25.0, 26.1, 26.5, 26.6, 27.2, 28.5, 31.6, 33.9, 34.1, 35.1, 37.7, 38.8, 41.2, 43.6, 43.9, 45.4, 45.9, 46.4, 48.1, 51.1, 60.4, 61.5, 121.1, 126.5, 128.0, 128.2, 130.7, 134.2, 135.2, 137.4, 142.5, 143.3, 156.9, 157.0, 157.9, 160.2, 164.2; **IR**: *v* 2919, 1649, 1384 cm^{-1}; **HRMS** calcd. for $C_{45}H_{62}N_5OSi^+$ [M +H^+]: 716.4724. Found: 716.4721.

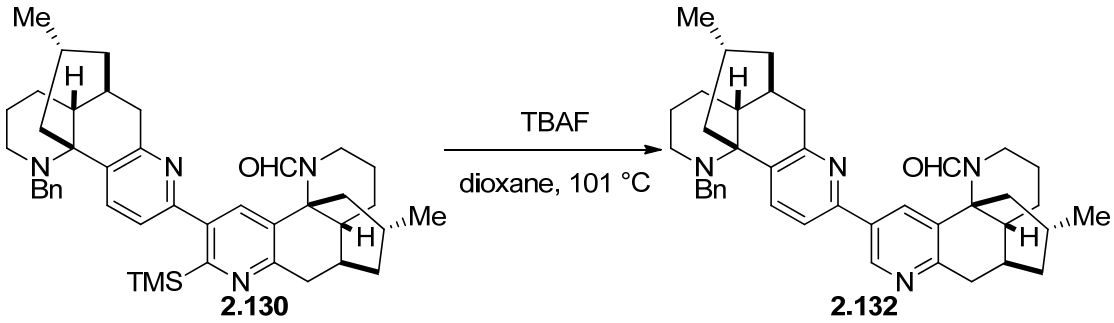
2.129: $[\alpha]^{23.0}_{D}$ +27.4° (*c* 0.73, CH_2Cl_2); R_f = 0.40 (silica gel, hexanes/EtOAc = 5/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.12 (s, 9H), 0.78 (d, *J* = 5.6 Hz, 3H), 0.80 (d, *J* = 5.6 Hz, 3H), 0.83-0.88 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 1H), 1.18-1.59 (m, 13H), 1.71-1.79 (m, 2H), 1.92-2.01 (m, 2H), 2.13 (brs, 2H), 2.39-2.43 (m, 1H), 2.53-2.55 (m, 2H), 2.76 (t, *J* = 18.8 Hz, 2H), 2.92-3.10 (m, 8H), 3.16-3.29 (m, 2H), 4.11 (d, *J* = 14.4 Hz, 1H), 4.25 (d, *J* = 14.4 Hz, 1H), 7.25-7.27 (m, 1H), 7..34-7.38 (m, 3H), 7.50 (d, *J* = 7.2 Hz, 2H), 8.14-8.17 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 0.26, 14.1, 21.3, 22.3, 22.4, 25.3, 26.0, 26.5, 26.8, 27.2, 31.6, 34.1, 34.2, 34.7, 35.25, 35.30, 38.8, 43.0, 43.6, 43.9, 45.5, 46.0, 46.2, 48.1, 51.1, 60.3, 61.8, 121.1, 126.5, 128.0, 128.2, 133.6, 133.9, 135.1, 136.4, 141.2, 142.6, 156.9, 157.4, 157.6, 163.5, 164.0; **IR**: *v* 3446, 2918, 1652, 732 cm^{-1}; **HRMS** calcd. for $C_{45}H_{62}N_4OSi^+$ [M +H^+]: 716.4724. Found: 716.4727



In a pressure tube pyridyl alkyne **2.80** (15.6 mg, 36 μmol, 1.0 equiv.), alkyne-nitrile **2.120** (12.9 mg, 52 μmol, 1.4 equiv.), and triphenylphosphine (79 mg, 0.30 mmol, 8.4 equiv.) were dissolved in freshly-degassed dioxane (8 mL). Neat $CpCo(CO)_2$ (10 μL, 80 μmol, 2.2 equiv.) was added and the tube was sealed. The resulting solution was placed in a 140 °C oil bath. After 24 hours the reaction was cooled to 23 °C and concentrated. The crude material was purified by silica gel chromatography (20/1 → 2/1 hexanes/EtOAc) to afford bipyridyls **2.130** (10.2 mg, 42%) and **2.131** (3.4 mg, 14%) both as yellow oils.

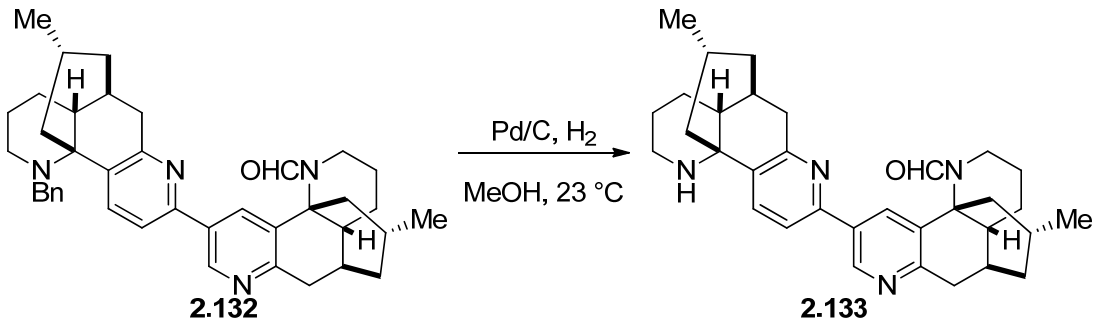
2.182: $[\alpha]^{24}_{D}$ +26.6° (*c* 0.50, CH_2Cl_2); R_f = 0.35 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.12 (s, 9H), 0.74 (d, *J* = 6.0 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 1.15-1.18 (m, 1H), 1.24-1.32 (m, 4H), 1.35-1.69 (m, 10H), 1.74-1.84 (m, 4H), 1.93-1.96 (m, 2H), 2.05 (s, 1H), 2.11-2.15 (m, 1H), 2.21-2.32 (m, 1H), 2.52-2.54 (m, 1H), 2.76 (d, *J* = 40.0 Hz, 1H), 2.82 (d, *J* = 40.4 Hz, 1H), 3.20-3.31 (m, 2H), 4.18 (dd, *J* = 13.6 and 54.8 Hz, 2H), 4.55-4.59 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.46-7.53 (m, 2H), 7.59 (s, 1H), 7.55-7.70 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.72 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 0.8, 21.2, 22.2, 22.3, 25.4, 25.8, 26.5, 26.7, 27.2, 33.6, 34.0, 35.0, 35.1, 37.2, 38.6, 42.8, 43.8, 44.2, 45.8, 46.5, 48.1, 51.0, 60.4, 61.8, 121.0, 126.5, 128.0, 128.2, 128.5, 131.4, 131.9, 135.3, 137.9, 140.6, 142.3, 156.4, 157.3, 160.5, 161.3; **IR**: *v* 1653, 1386, 838 cm^{-1}; **HRMS** calcd. for $C_{43}H_{57}N_4OSi^+$ [M+H$^+$]: 673.43016. Found: 673.43002.

2.183: $[\alpha]^{24}_{D}$ +35.2° (*c* 0.40, CH_2Cl_2); R_f = 0.28 (silica gel, hexanes/EtOAc = 2/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.09 (s, 9H), 0.79 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 1.18-1.65 (m, 11H), 1.71-1.87 (m, 5H), 1.93-1.98 (m, 2H), 2.13-2.16 (m, 1H), 2.22-2.24 (m, 1H), 2.29-2.42 (m, 2H), 2.51-2.55 (m, 2H), 2.73 (d, *J* = 18.8 Hz, 1H), 2.87 (d, *J* = 18.8 Hz, 1H), 2.96-3.12 (m, 1H), 3.21-3.29 (m, 2H), 4.18 (dd, *J* = 14.4 and 64.8 Hz, 2H), 4.50-4.54 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.23-7.27 (m, 1H), 7.34-7.38 (m, 3H), 7.49 (d, *J* = 7.6 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.66 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -0.1, 0.8, 21.1, 22.2, 22.4, 25.4, 25.8, 26.5, 26.6, 27.2, 33.7, 34.1, 34.9, 35.3, 37.3, 38.5, 42.8, 43.8, 44.2, 45.9, 46.4, 48.2, 50.9, 60.3, 62.0, 121.6, 126.5, 128.0, 128.2, 131.0, 131.4, 135.1, 137.2, 142.1, 142.4, 155.9, 156.6, 157.9, 160.6, 164.8; **IR**: *v* 1657, 1652, 1386, 839, 733 cm^{-1}; **HRMS** calcd. for $C_{43}H_{57}N_4OSi^+$ [M+H$^+$]: 673.43016. Found: 673.43030.



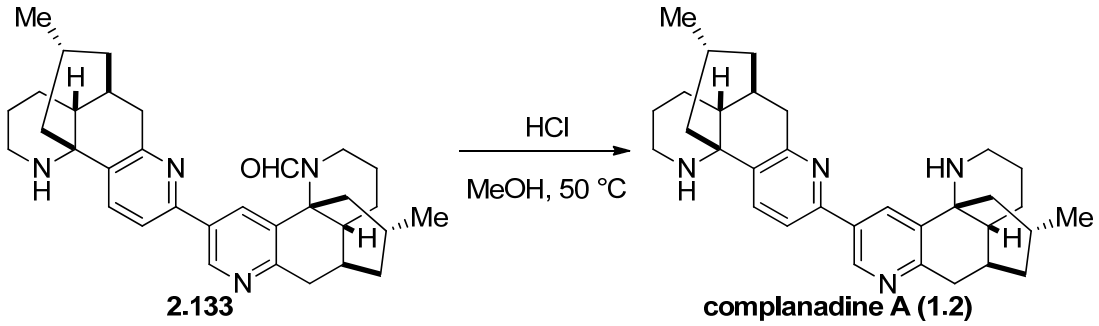
To a solution of bipyridyl **2.130** (36 mg, 0.053 mmol, 1.0 equiv.) in dioxane (1 mL) was added TBAF solution (1.0 M in THF, 200 μL, 0.20 mmol, 3.8 equiv.) and the mixture was placed in a 120 ºC oil bath. After 10 hours the solution was cooled to 23 °C, diluted with saturated NH_4Cl solution (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (20/1 → 1/1 hexanes/EtOAc) to afford amine **2.132** (32.0 mg, 99%) as dark yellow oil.

2.132: $[\alpha]^{24}_D$ +35.1° (*c* 0.40, CH_2Cl_2); R_f = 0.22 (silica gel, hexanes/EtOAc = 1/1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.69 (d, *J* = 6.0 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 1.09-1.38 (m, 6H), 1.43-1.80 (m, 12H), 1.88 (td, *J* = 3.6 and 12.8 Hz, 1H), 1.97-2.09 (m, 2H), 2.17-2.27 (m, 2H), 2.41-2.45 (m, 2H), 2.72 (dd, *J* = 19.2 and 30.8 Hz, 2H), 3.18-3.27 (m, 2H), 4.11 (dd, *J* = 14.8 and 68.0 Hz, 2H), 4.48-4.52 (m, 1H), 7.18-7.20 (m, 1H), 7.27-7.31 (m, 2H), 7.41-7.45 (m, 3H), 7.83 (d, *J* = 2.4 Hz, 1H), 8.15 (d, *J* = 12.0 Hz, 1H), 8.68 (s, 1H), 8.89 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 22.1, 22.4, 25.4, 25.9, 26.5, 26.7, 27.1, 33.5, 34.0, 34.9, 35.5, 37.5, 38.5, 42.8, 43.7, 44.1, 45.8, 46.3, 48.2, 50.9, 60.4, 61.9, 118.9, 126.5, 128.0, 128.2, 131.5, 133.4, 134.4, 135.4, 137.7, 142.3, 146.7, 151.7, 157.8, 159.3, 160.5; **IR**: ν 1653, 1443, 1385, 733 cm^{-1}; **HRMS** calcd. for $C_{40}H_{49}N_4O^+$ [M+H$^+$]: 601.39064. Found: 601.39037.



To a solution of amine **2.132** (35 mg, 0.058 mmol, 1.0 equiv.) in methanol (1 mL) solid 5% palladium on carbon (20 mg) was added then rapidly stirred under H_2 (1 atm) at 23 °C. After 8 hours the solution was filtered through a celite pad and concentrated to afford formamide **2.133** (22.6 mg, 78 %) as pale brown oil.

2.133: $[\alpha]^{24}_{D}$ +25.2° (*c* 0.40, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.81 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 1.24-1.45 (m, 7H), 1.53-1.57 (m, 1H), 1.62-1.70 (m, 6H), 1.78-1.86 (m, 4H), 2.04-2.09 (m, 2H), 2.24-2.31(m, 3H), 2.66-2.73 (m, 1H), 2.80-2.86 (m, 2H), 3.10-3.34 (m, 3H), 4.57 (d, J = 5.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 8.28 (bs, 1H), 8.74 (s, 1H), 8.93 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5, 22.1, 24.6, 25.4, 25.9 (two peaks very close), 26.7, 32.9, 33.4, 34.9, 35.0, 37.5, 40.7, 41.4, 42.5, 42.7, 44.1, 44.4, 46.3, 47.4, 60.7, 61.9, 119.3, 131.6, 133.7, 134.7, 146.6, 153.4, 158.6, 158.8, 160.5, 170.0, 188.6; **IR**: v 3419, 1652, 1575, 1262, 910, 731 cm^{-1}; **HRMS** calcd. for $C_{33}H_{43}N_4O^+$ [M+H$^+$]: 511.34369. Found: 511.34377.



Formamide **2.133** (22.6 mg, 0.044 mmol, 1.0 equiv.) was dissolved in MeOH/HCl (conc.) solution (12/1, 1mL) and the reaction flask was placed in an oil bath heated to 50 °C. After 10 hours the solution was cooled to 23 °C, the acid was quenched with aqueous saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to afford crude complanadine A (**1.2**) (21.3 mg) as pale pink oil.

Additional purification was achieved as follows: from above complanadine A (**1.2**) (12 mg, 0.025mmol, 1 equiv.) was dissolved in aqueous 5% HCl solution (5 mL) and washed with Et_2O (2 × 5 mL), the aqueous layer was adjusted to a pH 13 with aqueous 10% NaOH solution, and the opaque solution was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to provide complanadine A (**1.2**) (10.8 mg, 90%) as colorless oil.

Complanadine A (1.2): $[\alpha]^{24}_{D}$ +14.5° (*c* 0.30, MeOH); **^{1}H NMR** (400 MHz, MeOH): δ 0.85 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 1.21-1.49 (m, 10H), 1.53-1.64 (m, 5H), 1.68-1.72 (m, 1H), 1.75-1.81 (m, 2H), 1.85-1.89 (m, 2H), 2.18-2.22 (m, 2H), 2.48-2.57 (m, 2H), 2.76-2.85 (m, 4H), 3.20-3.30 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.93 (s, 1H); **^{13}C NMR** (100 MHz, MeOH): δ 22.4, 27.1, 27.3, 27.7, 34.8, 34.9, 35.7, 36.2, 42.1, 44.7, 44.8, 44.9, 51.6, 51.7, 57.8, 57.9, 120.4, 133.7, 135.0, 135.9, 136.6, 137.6, 146.1, 153.7, 159.9, 160.5; **IR**: ν 2913, 1575, 1436 cm^{-1}; **HRMS** calcd. for $C_{32}H_{43}N_4^+$ [M+H$^+$]: 483.34877. Found: 483.34828.

We have found the optical rotation of complanadine A changes as the molecule transitions from the free base form to protonated forms.

Effects of acid addition on rotation:

–19.0° complanadine A free base

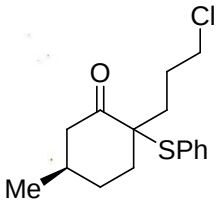
–9.5° complanadine A free base with 2 equiv TFA

–4.7° complanadine A free base with 4 equiv TFA

+2.4° complanadine A free base with 6 equiv TFA

and +10.5° complanadine A free base with 6 equiv HCl

2.8 Spectrum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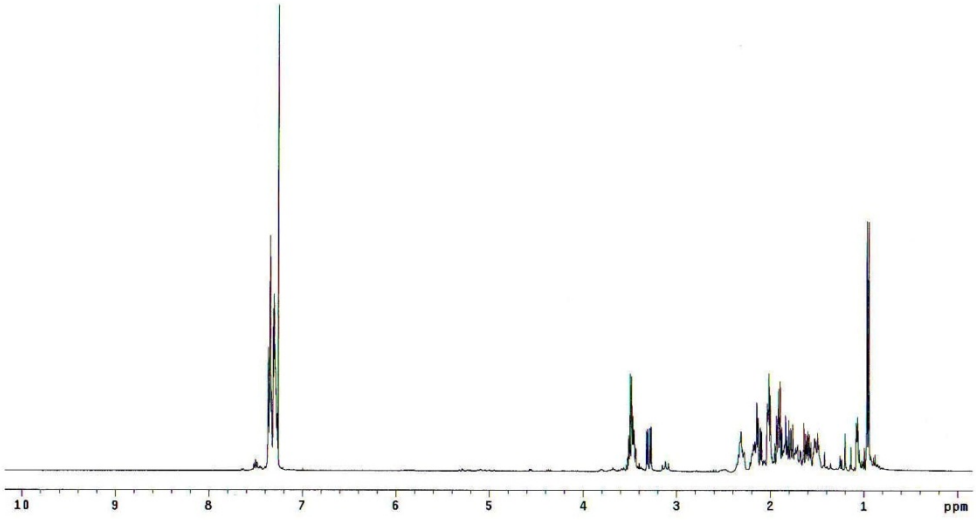
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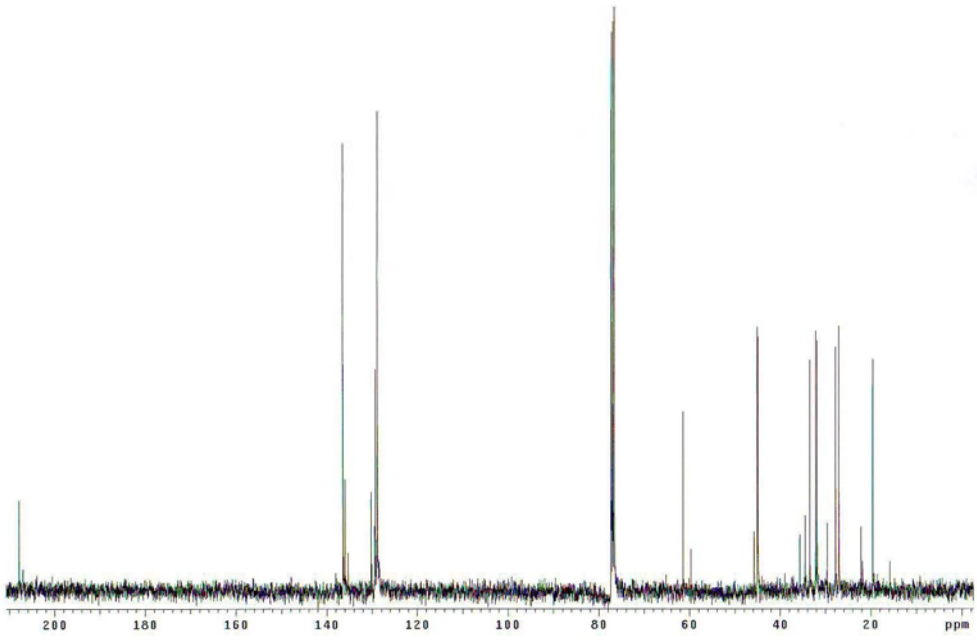
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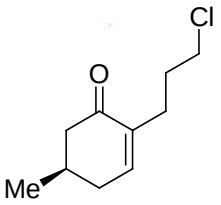
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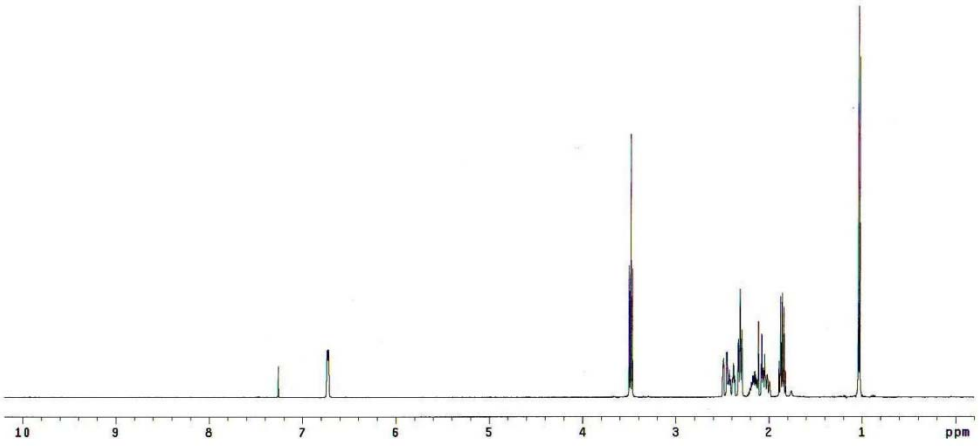
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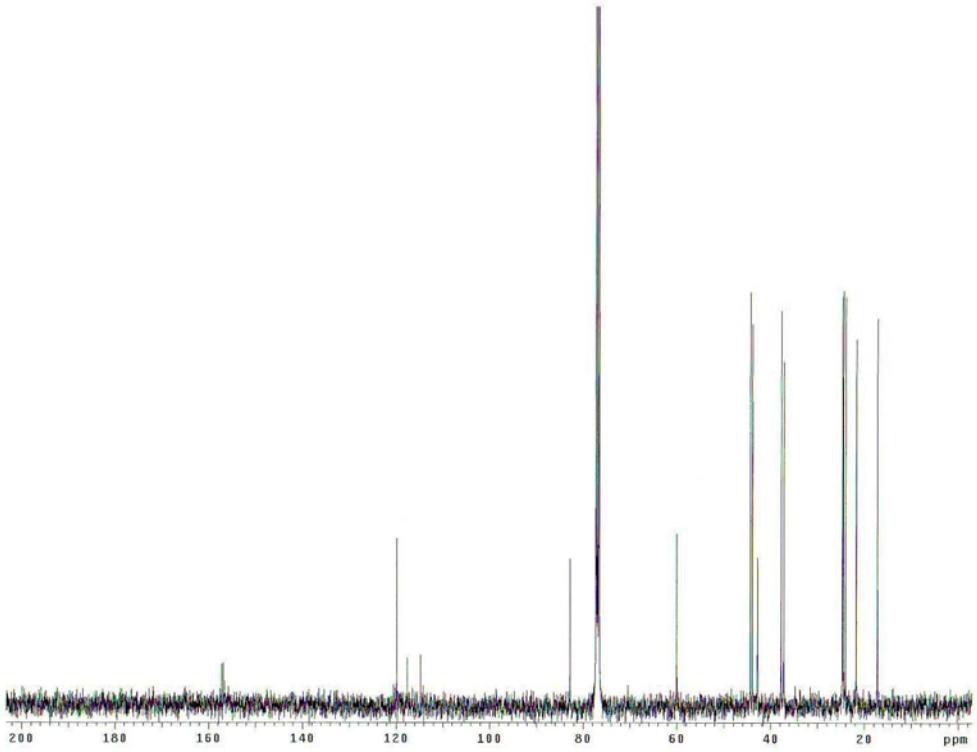
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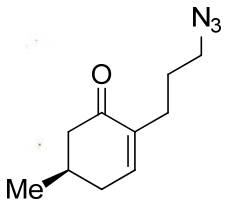
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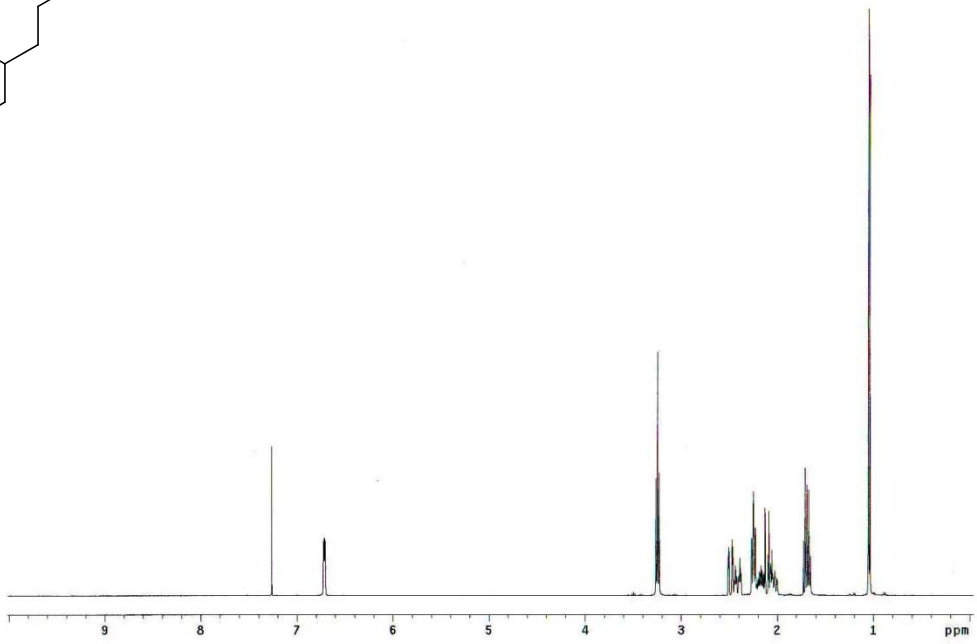
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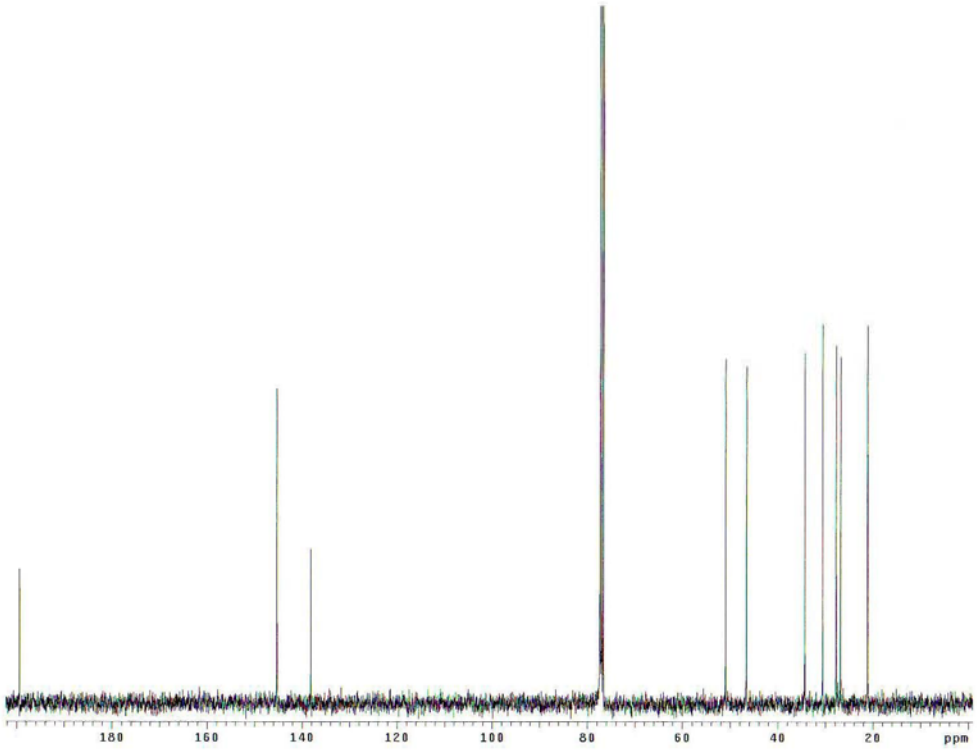
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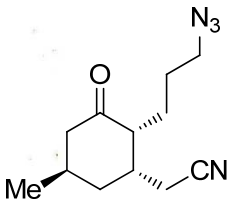
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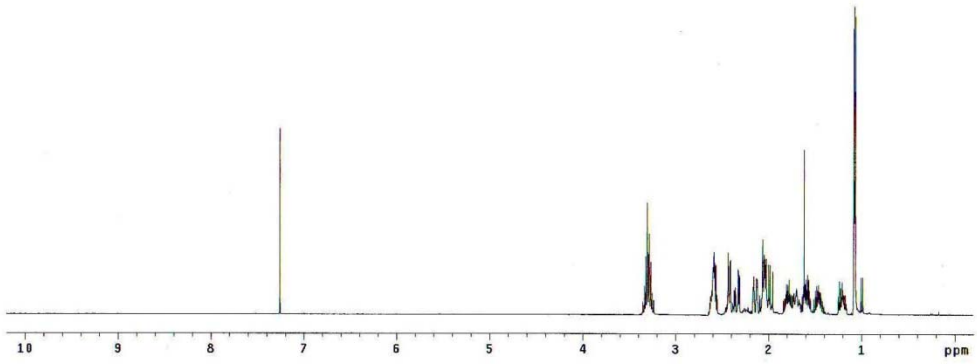
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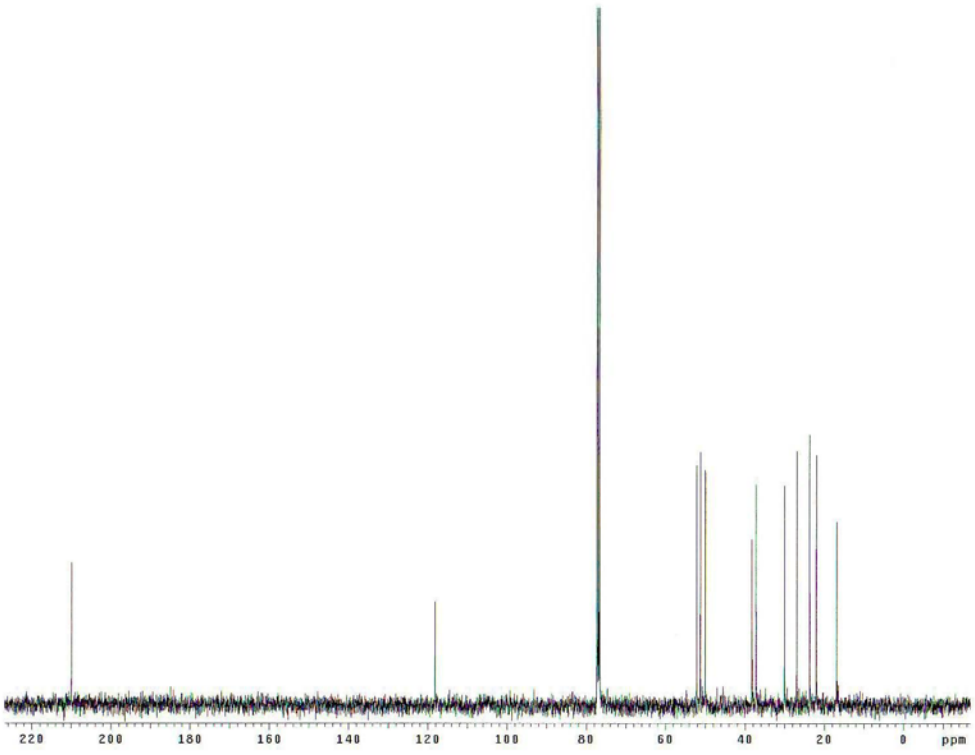
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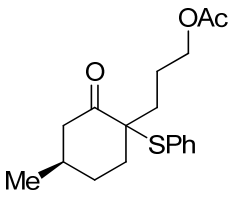
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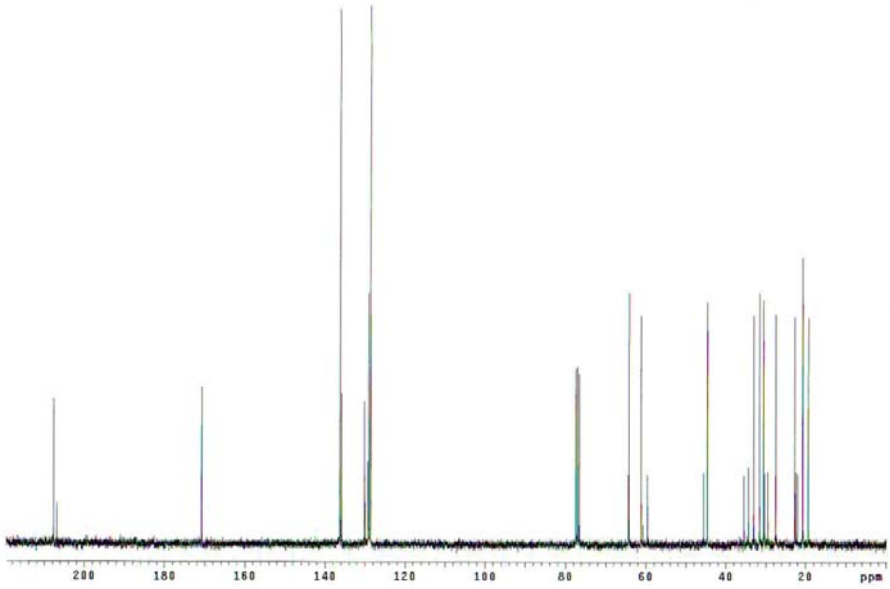
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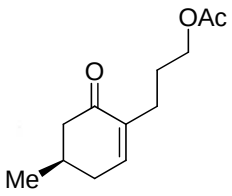
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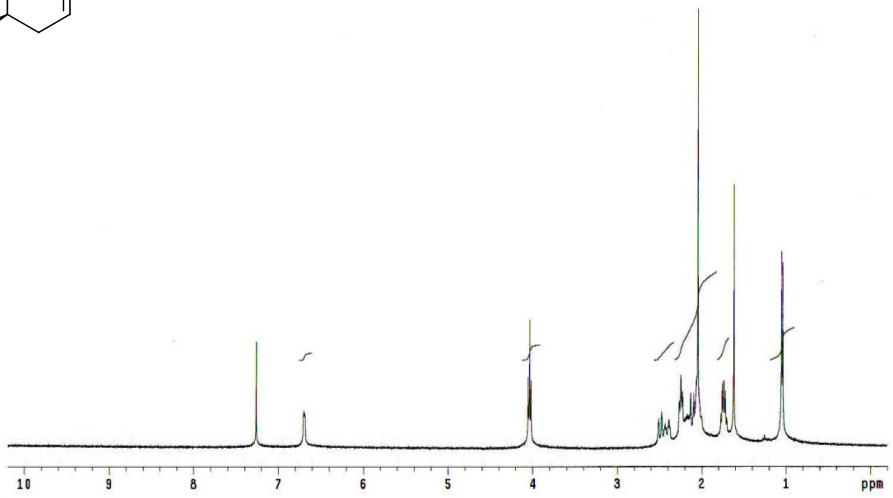
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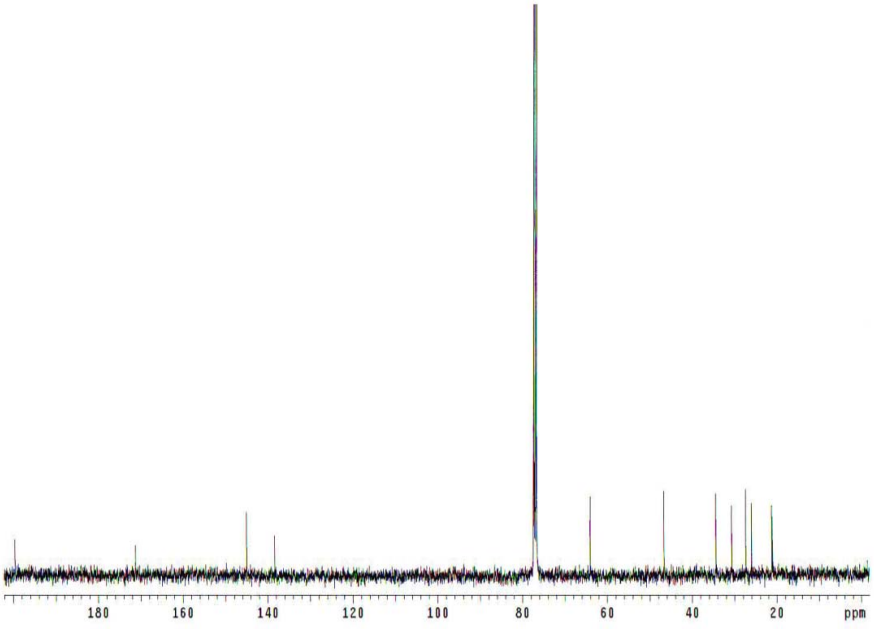
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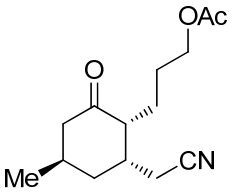
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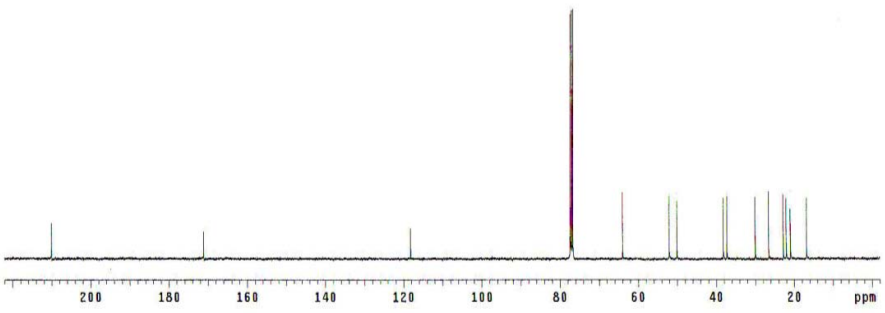
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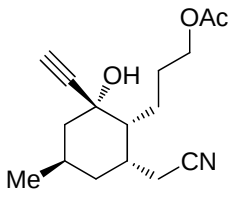
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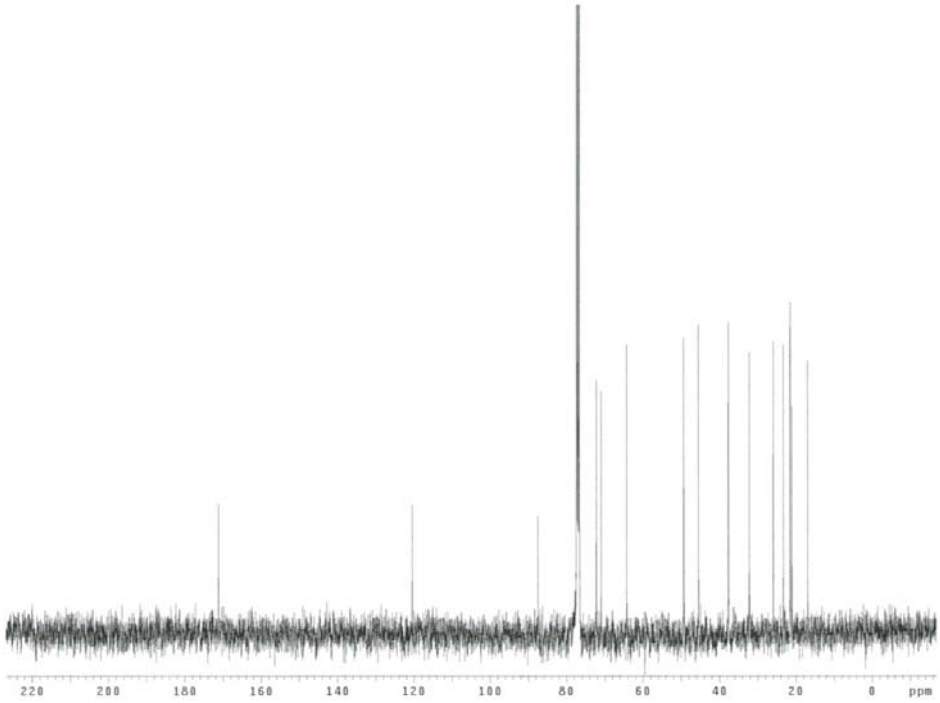
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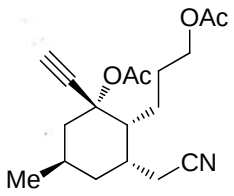
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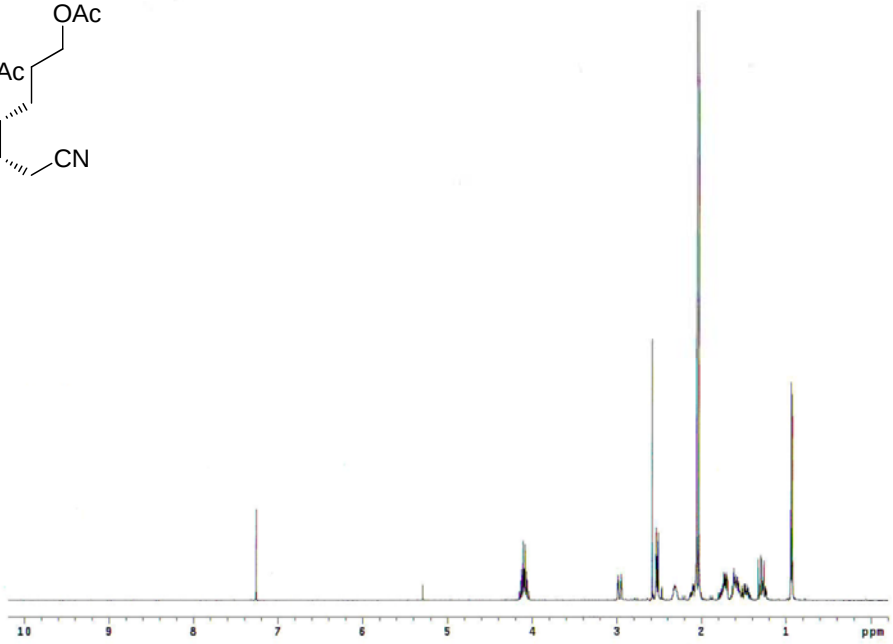
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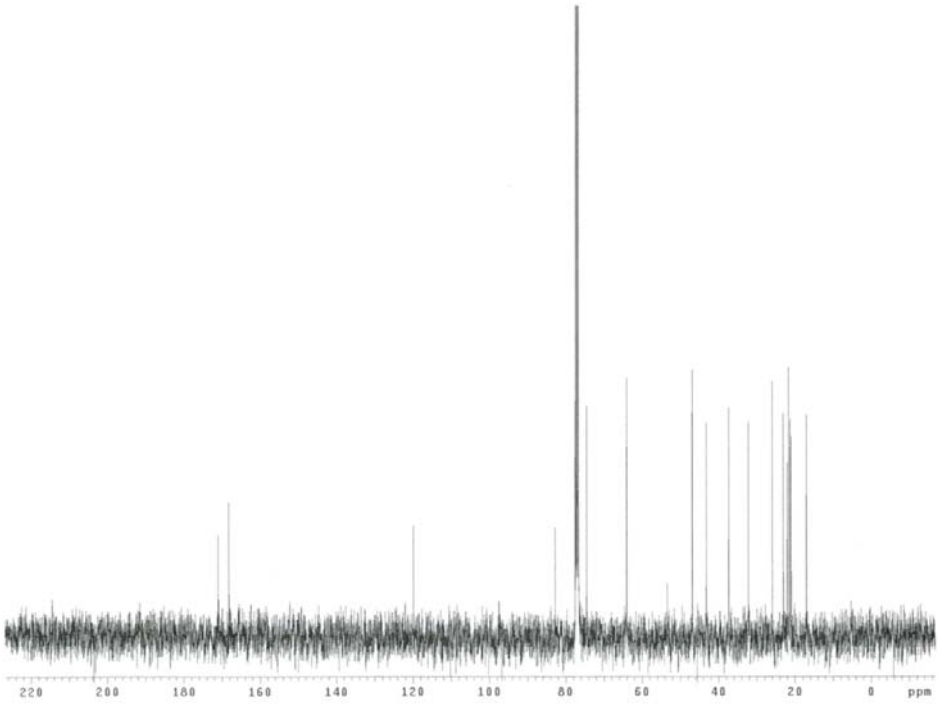
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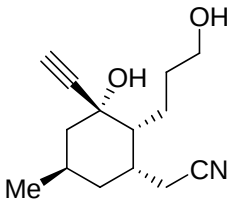
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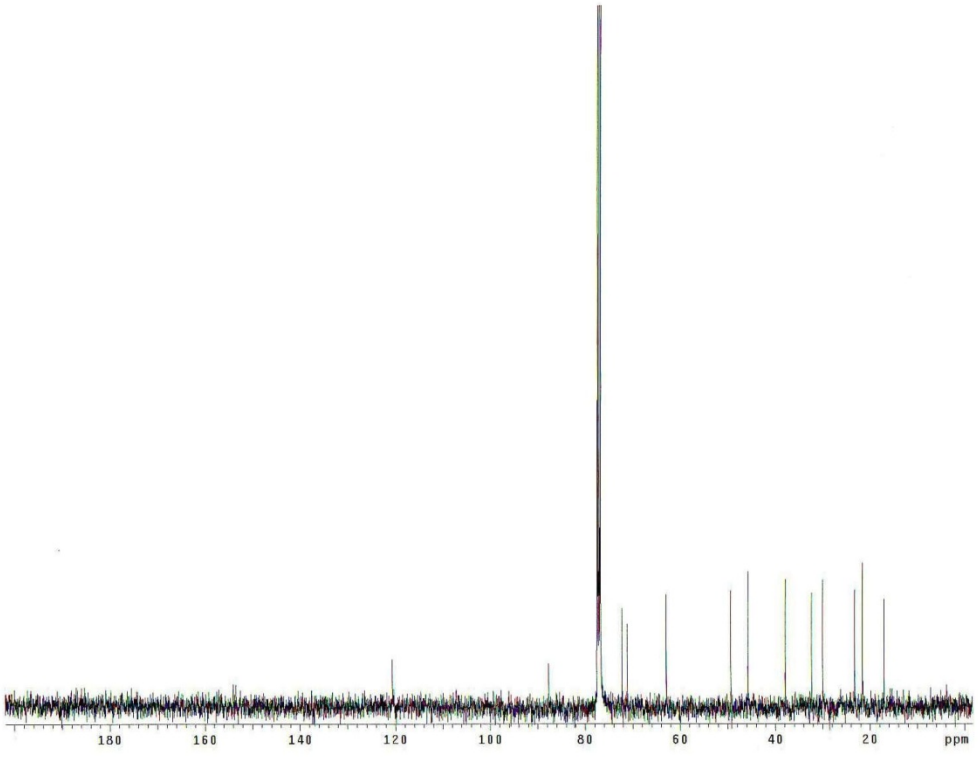
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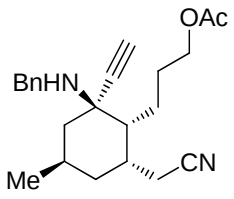
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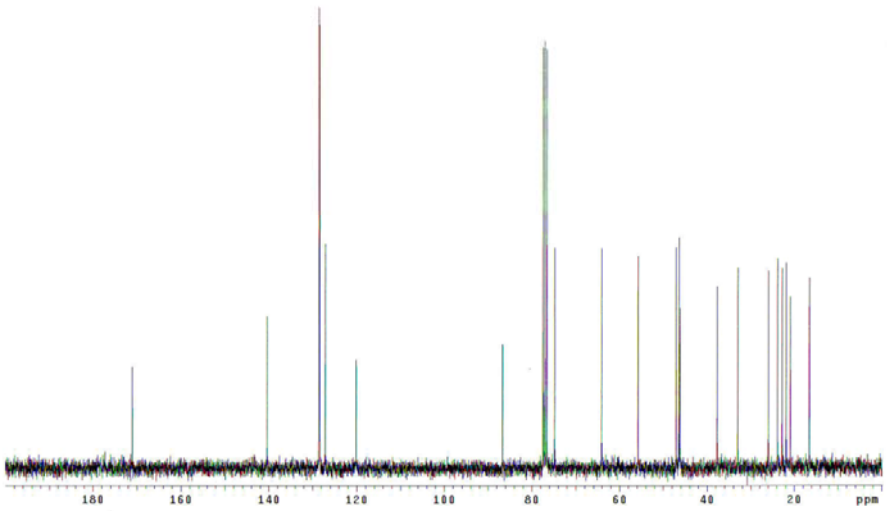
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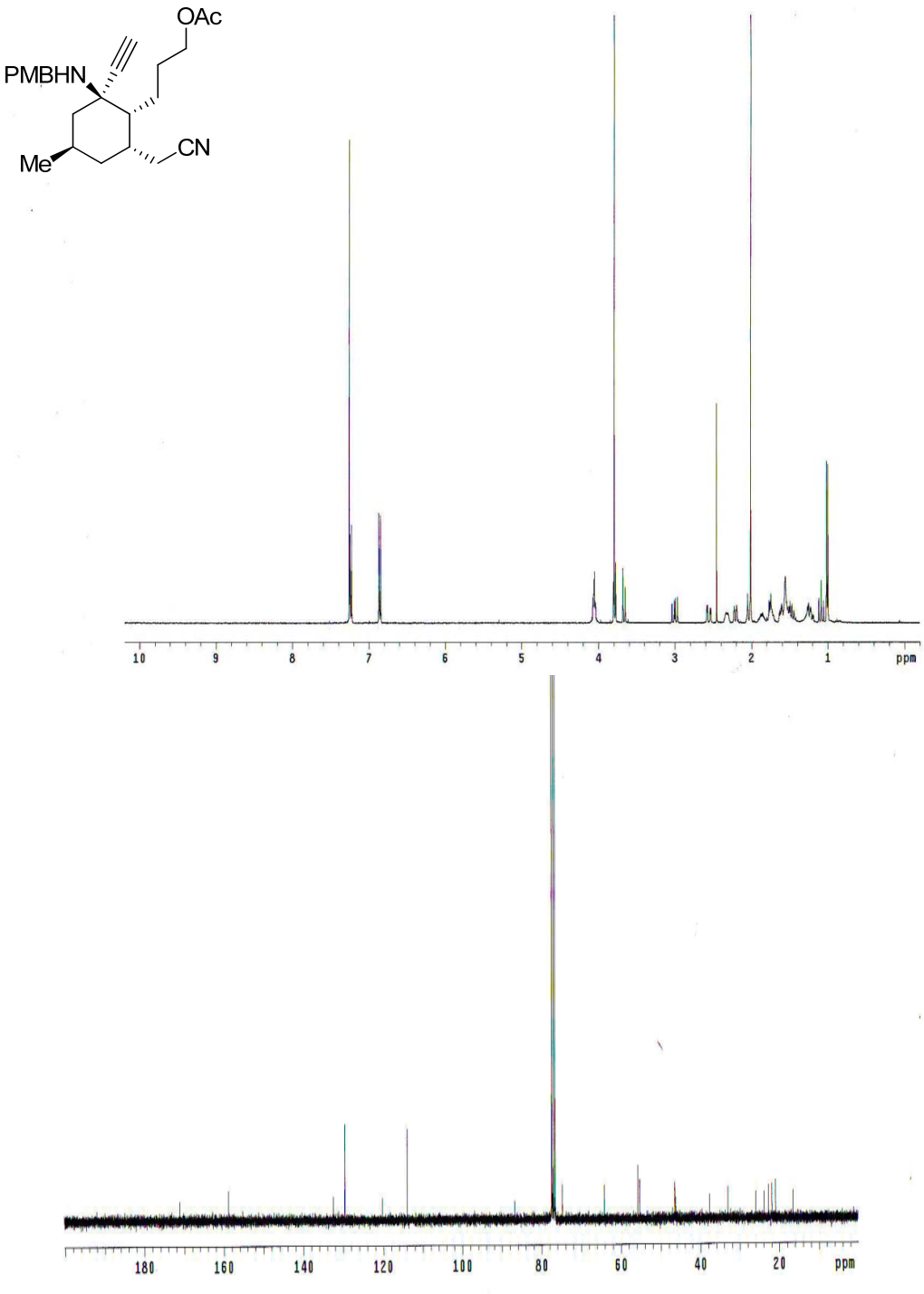
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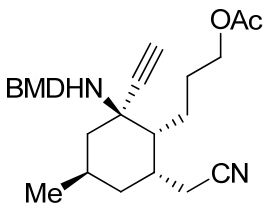
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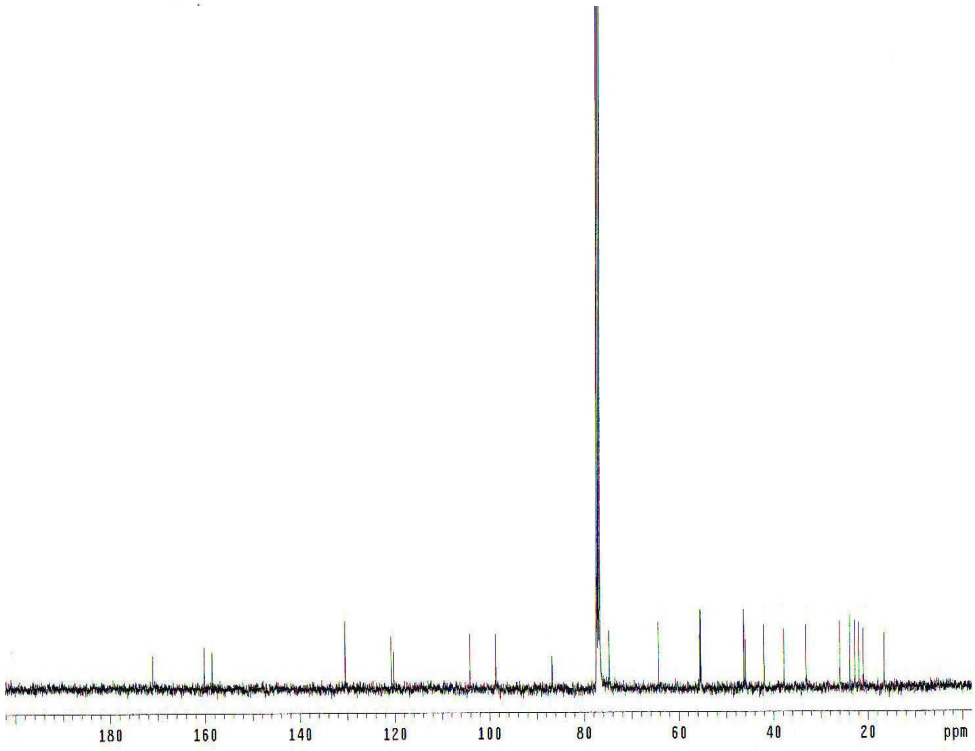
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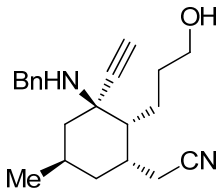
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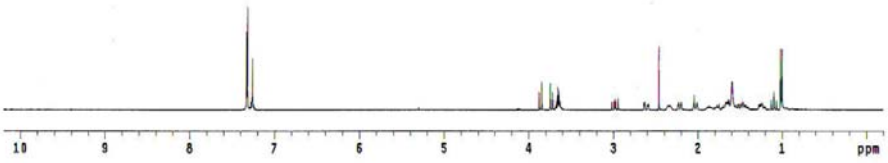
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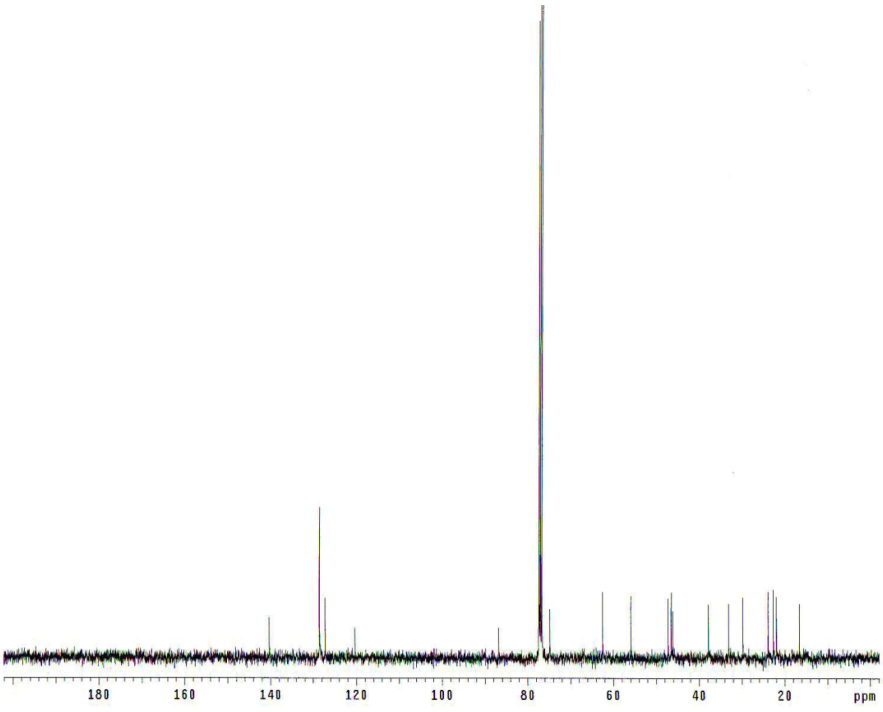
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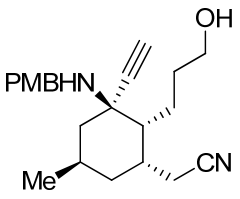
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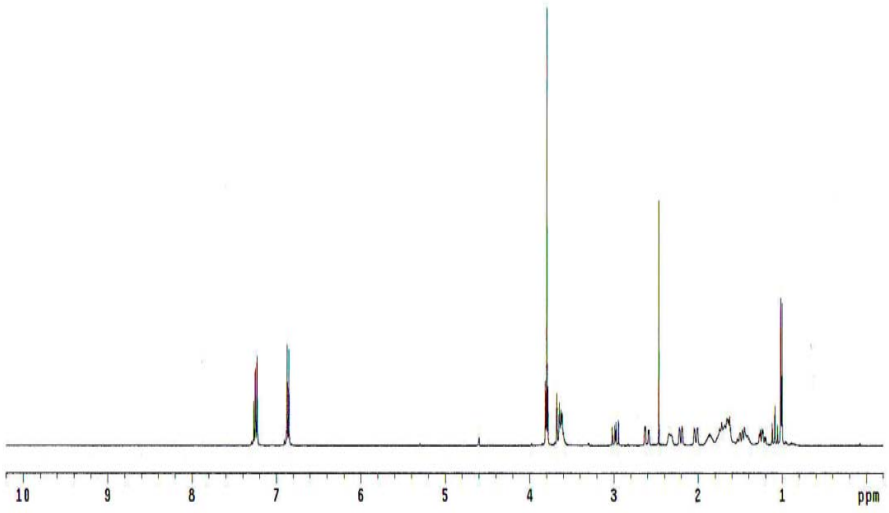
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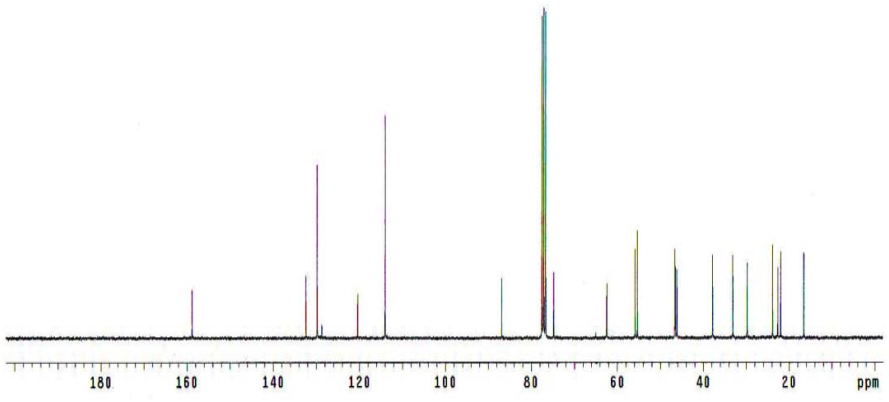
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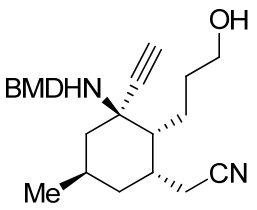
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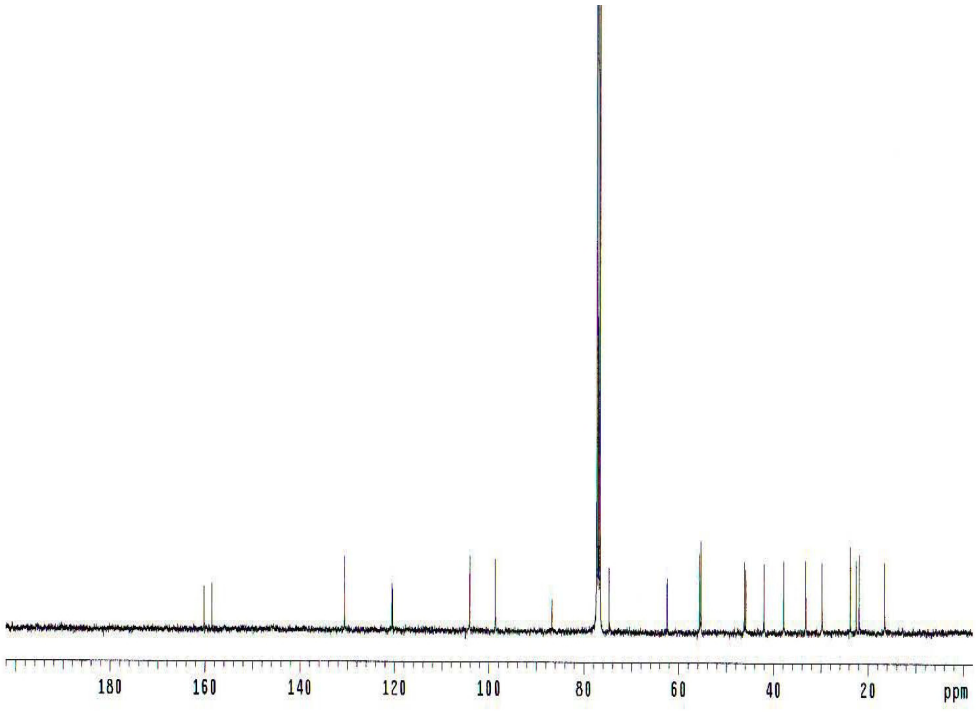
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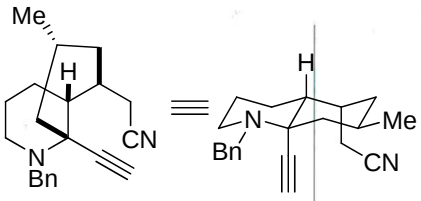
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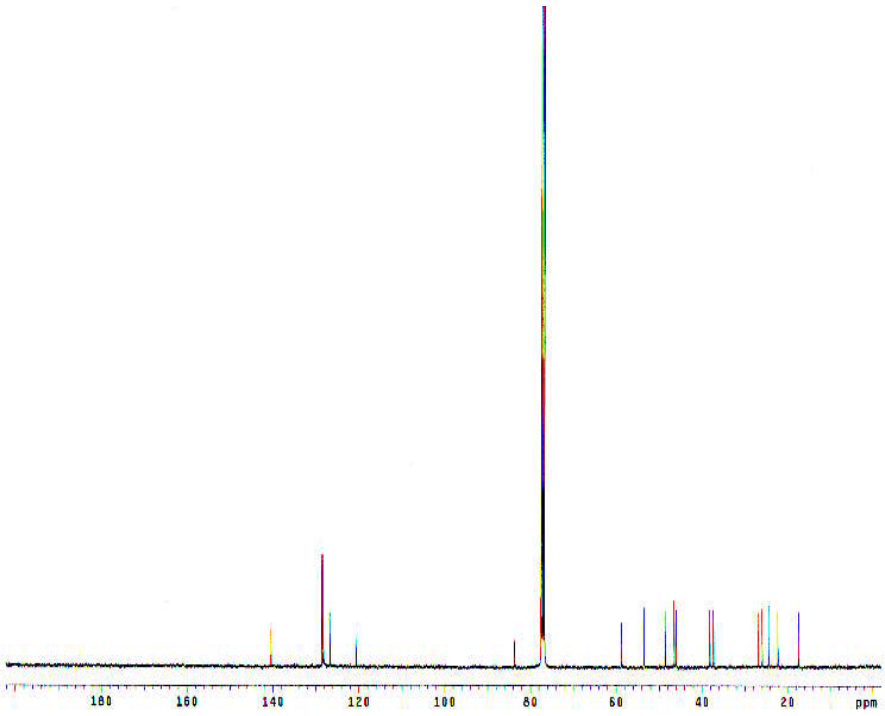
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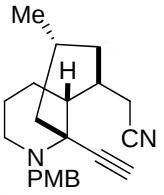
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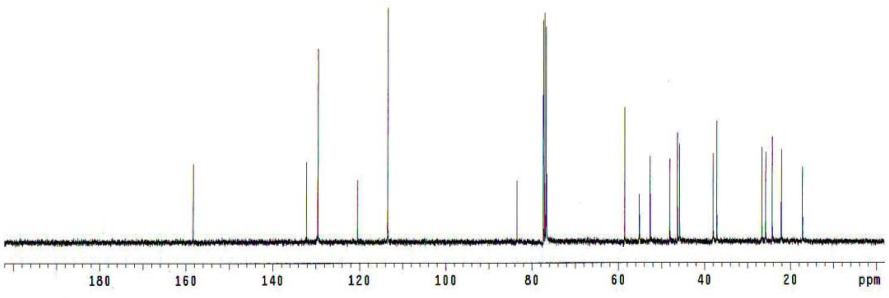
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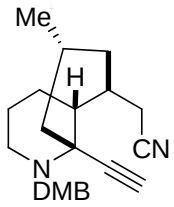
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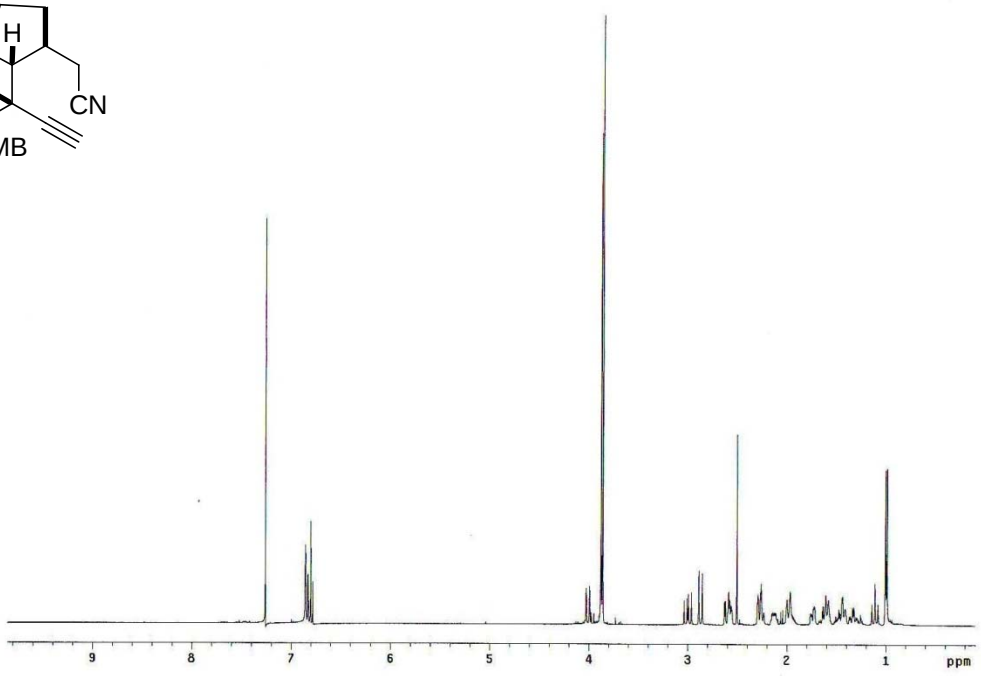
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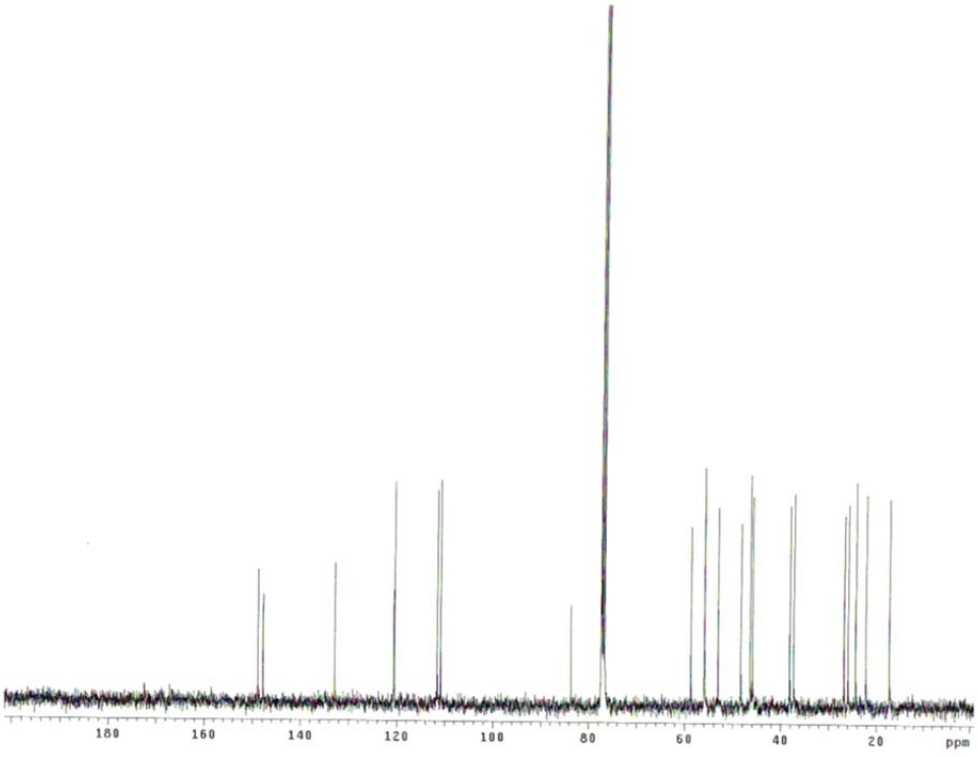
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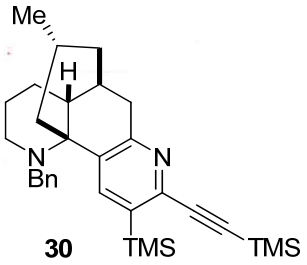
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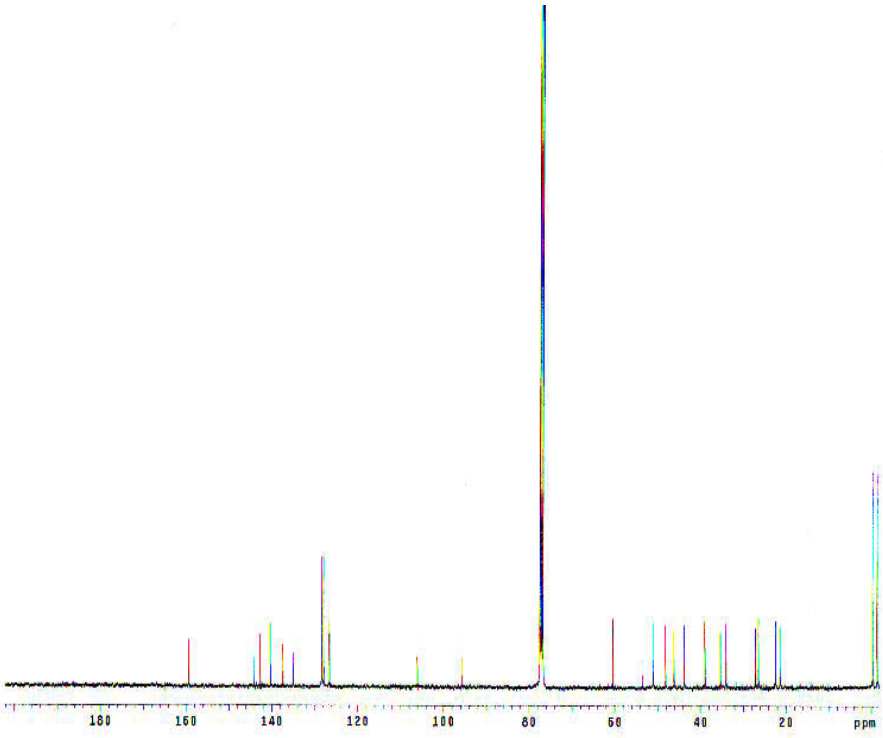
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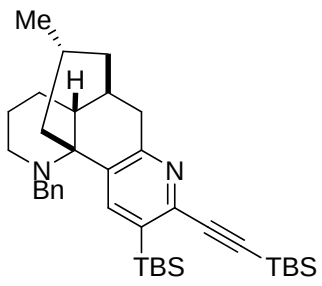
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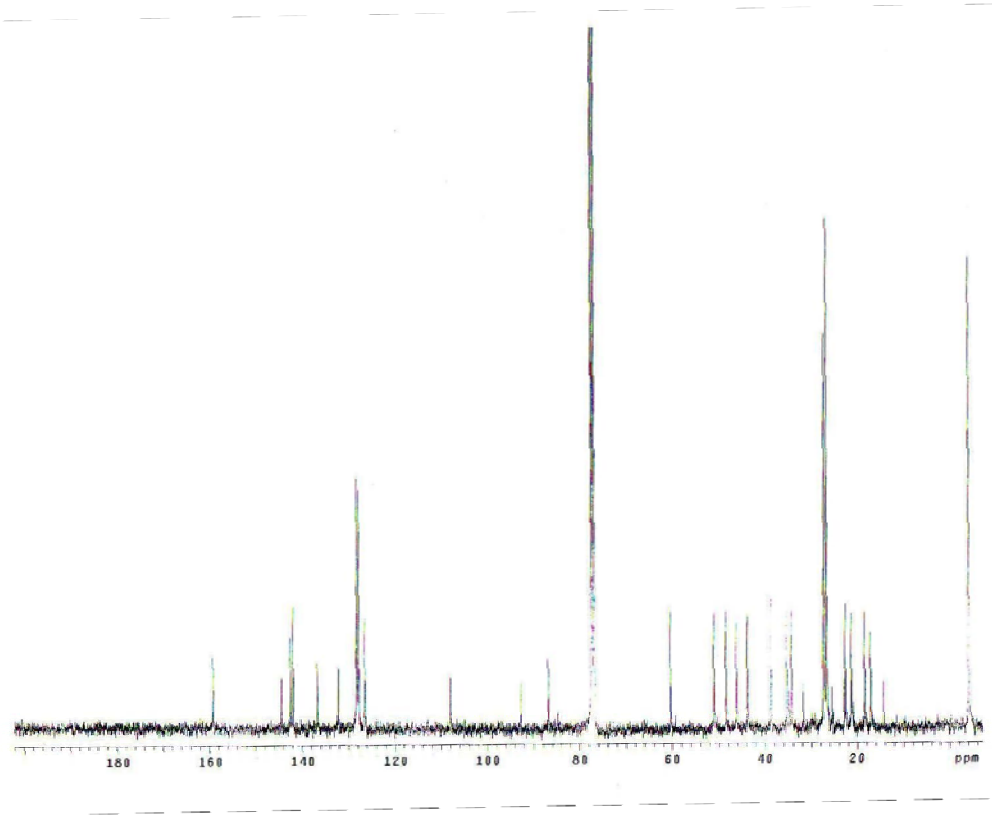
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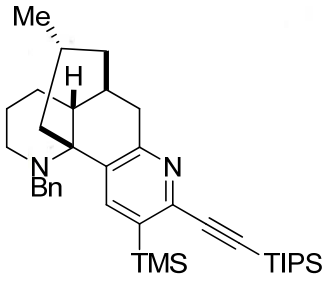
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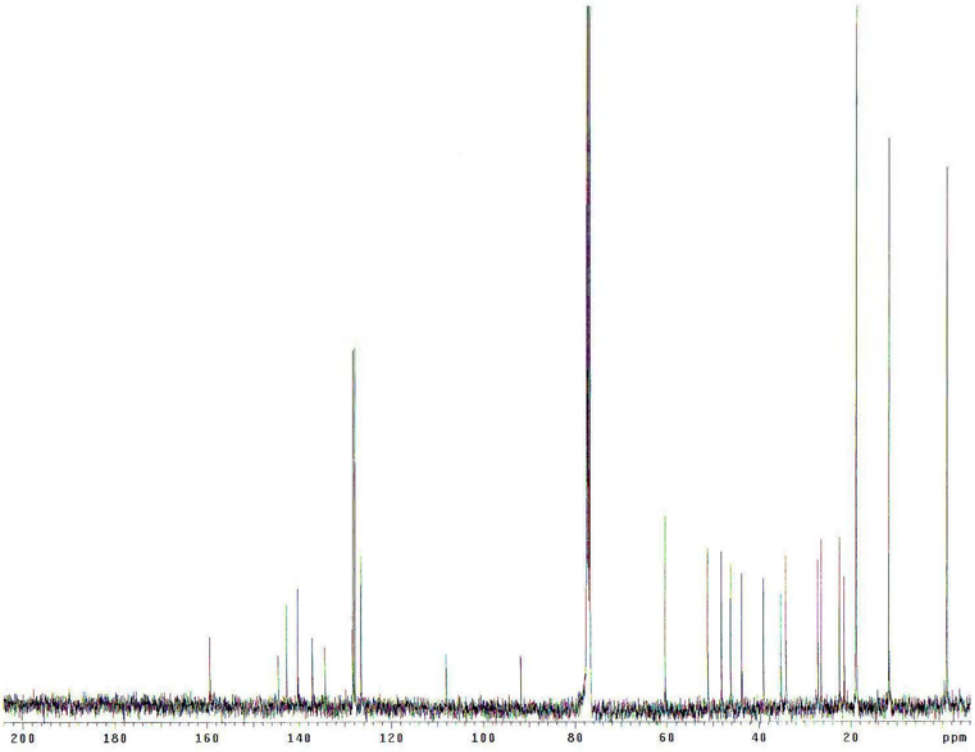
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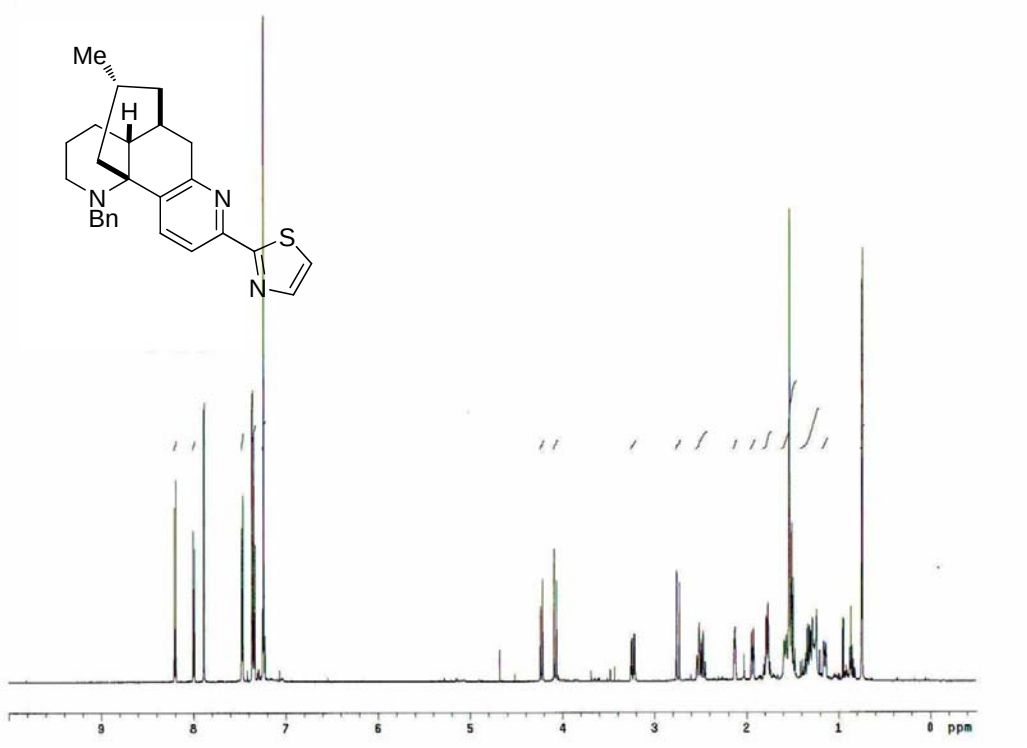
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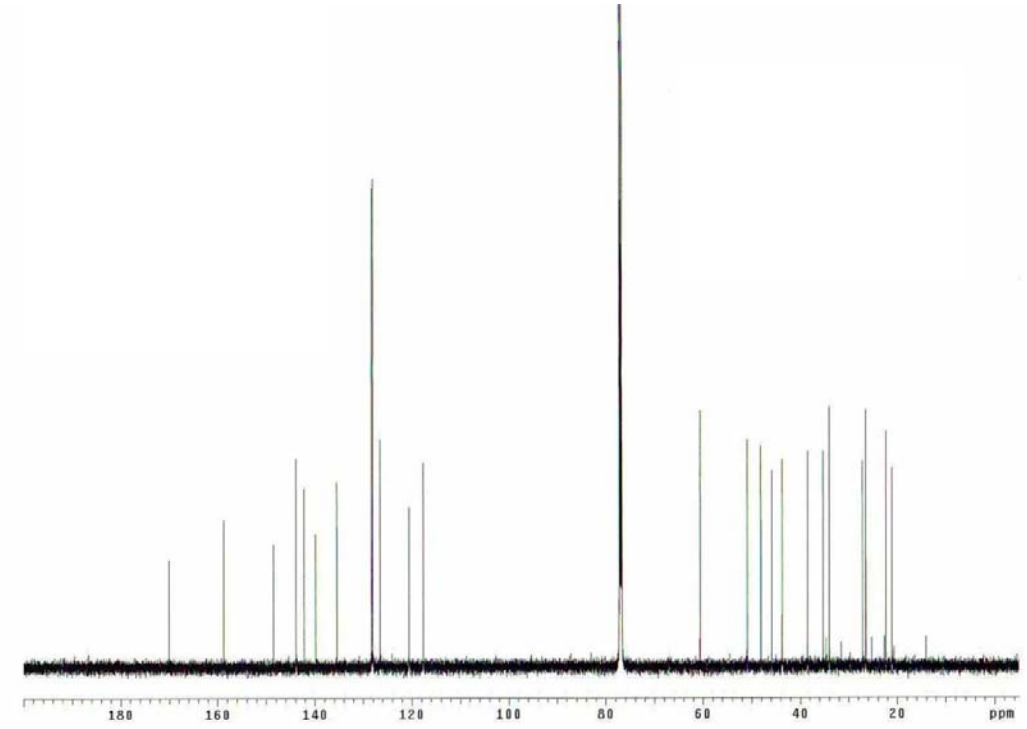
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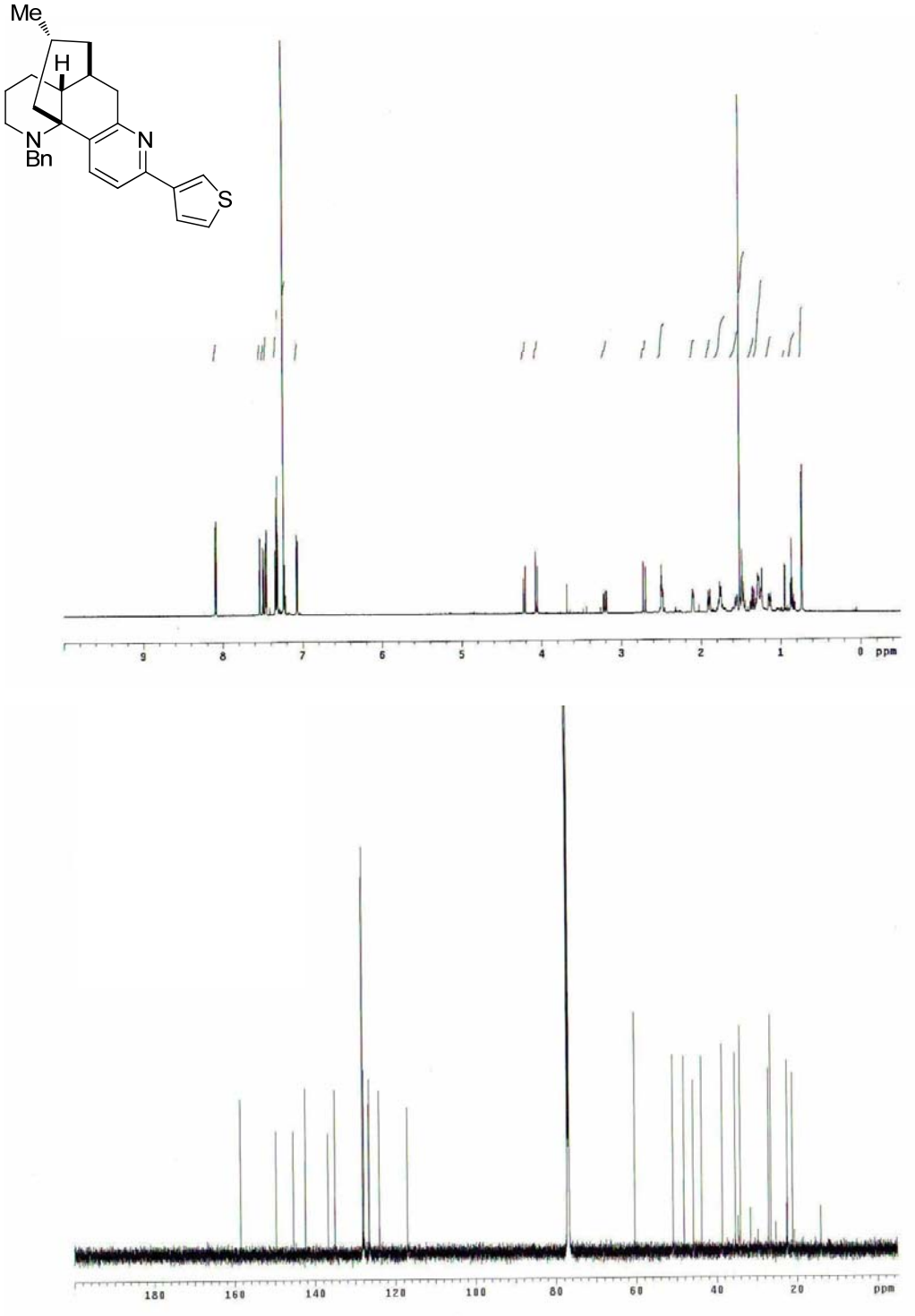
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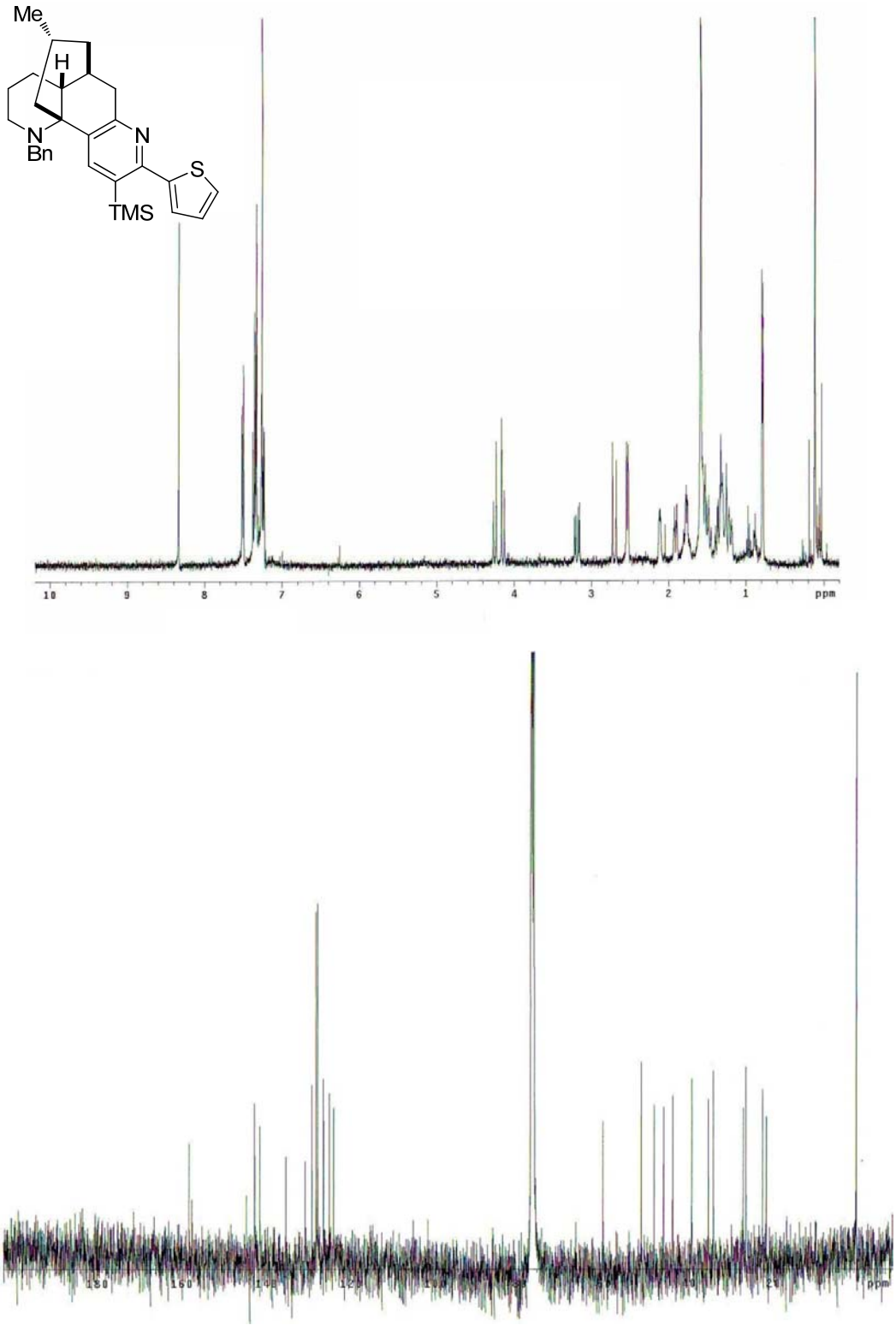
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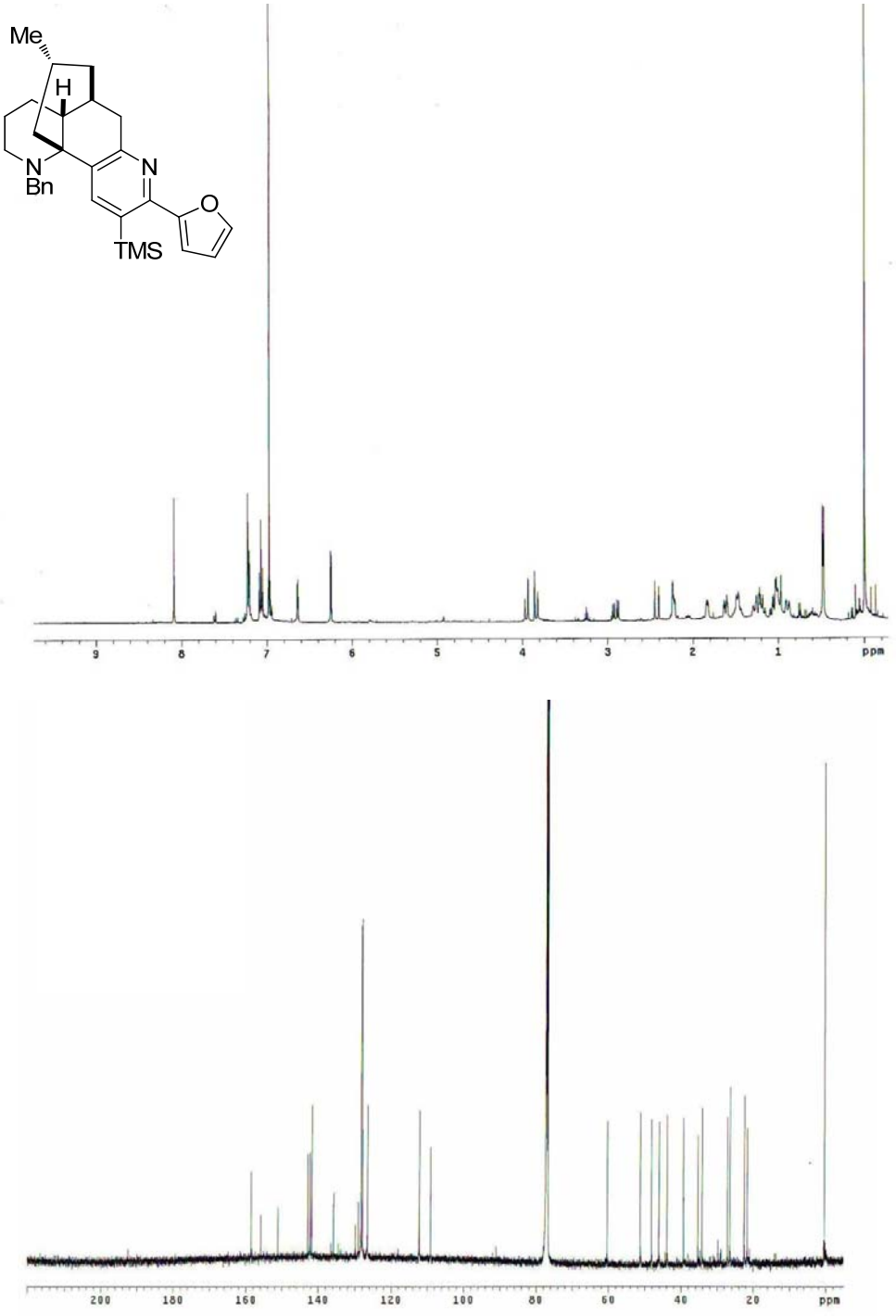
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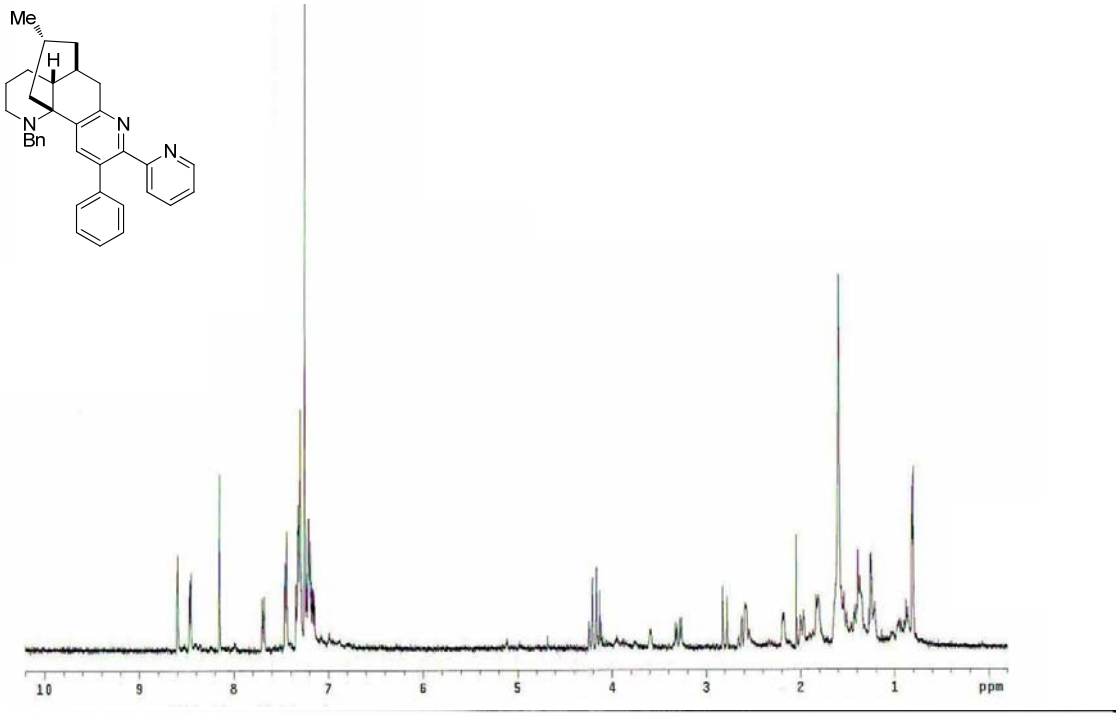
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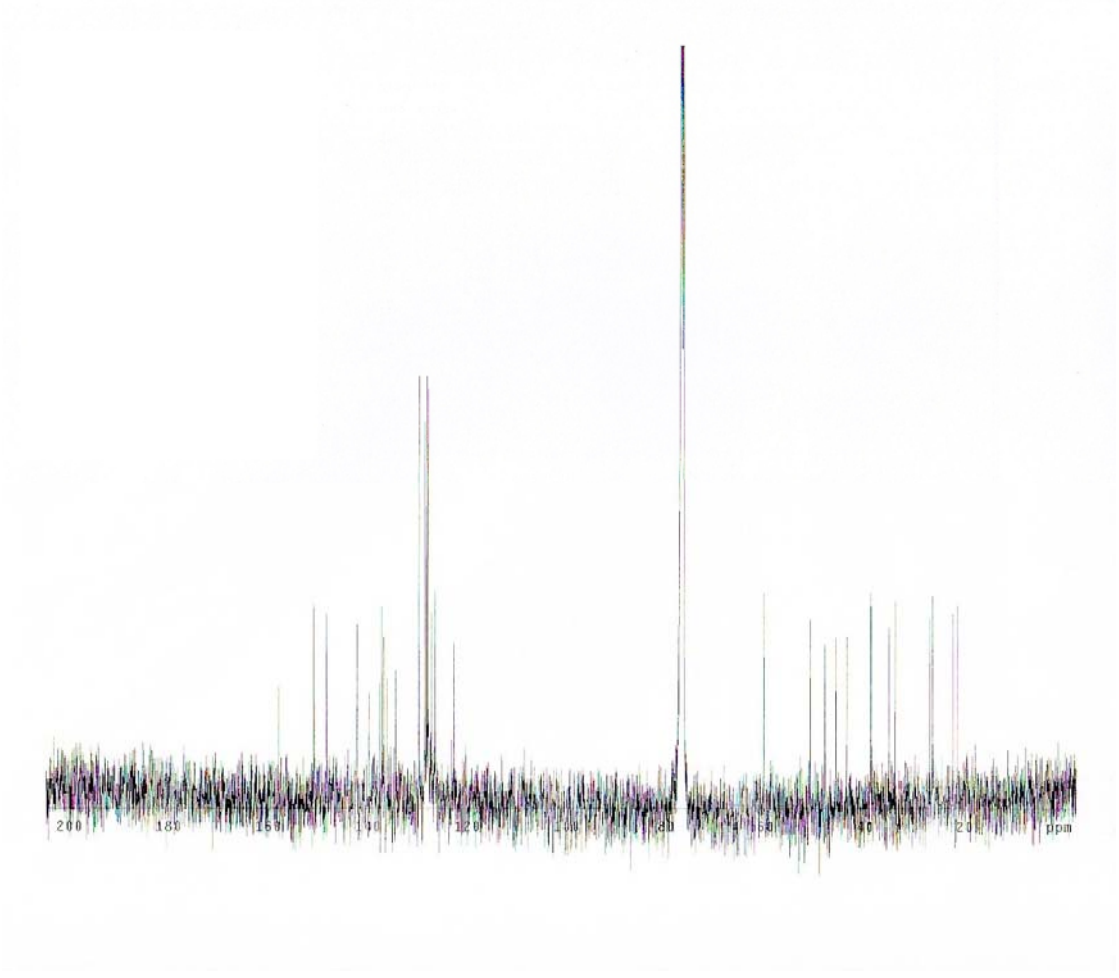
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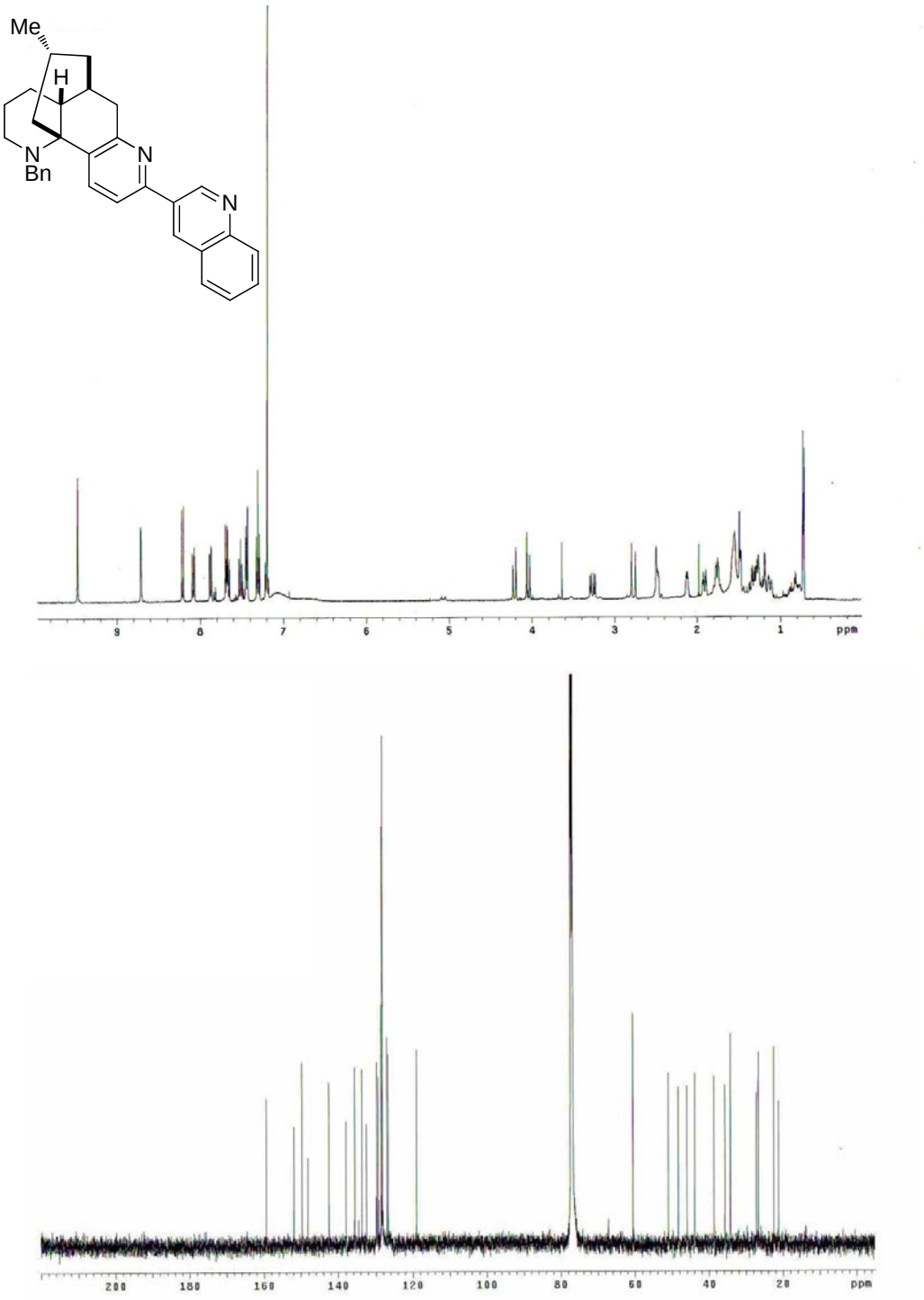
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Bn
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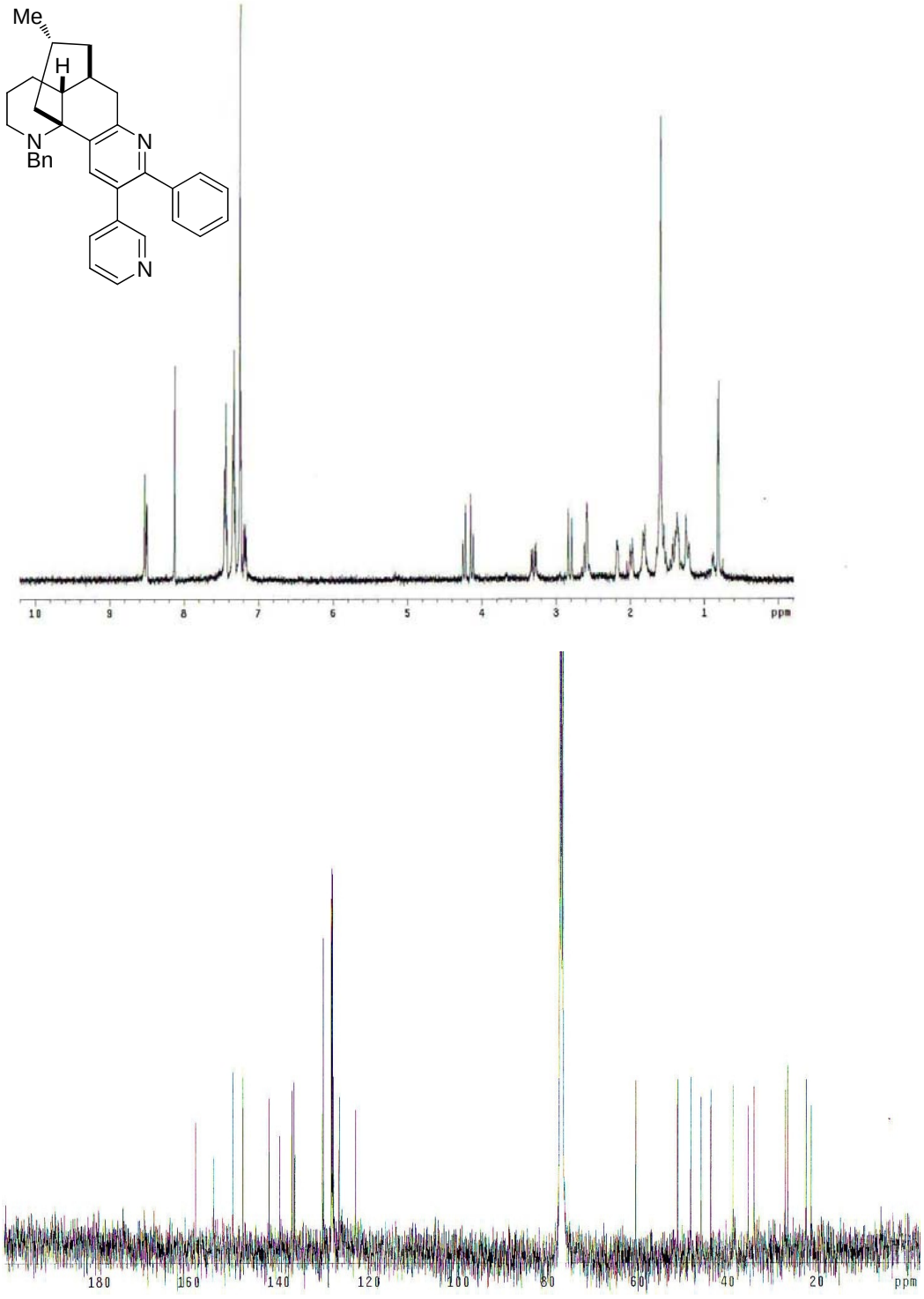
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ppm
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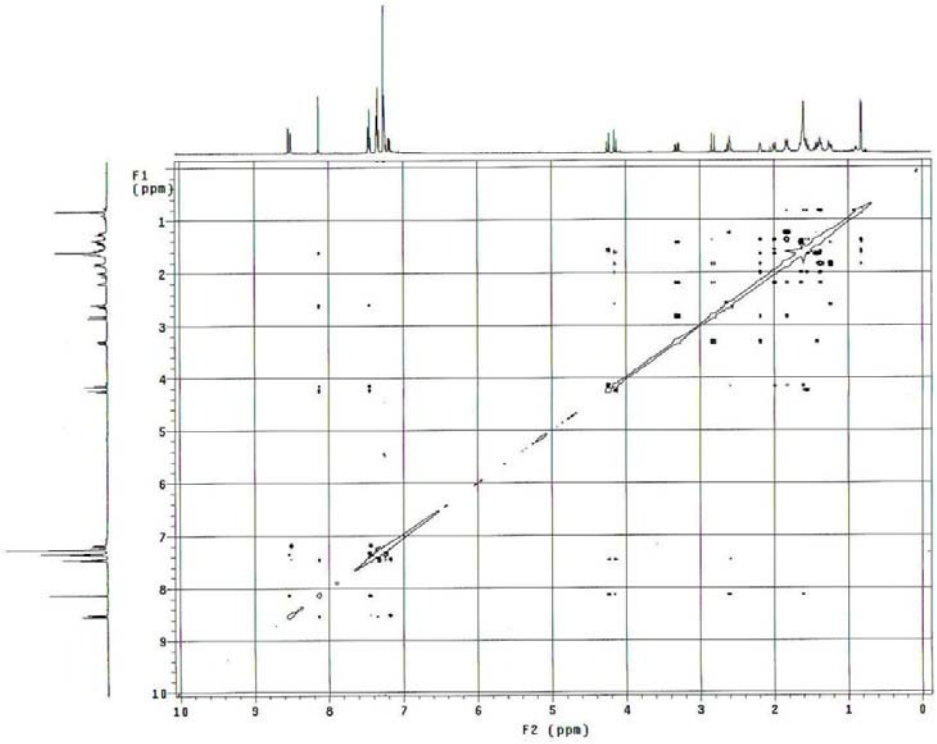
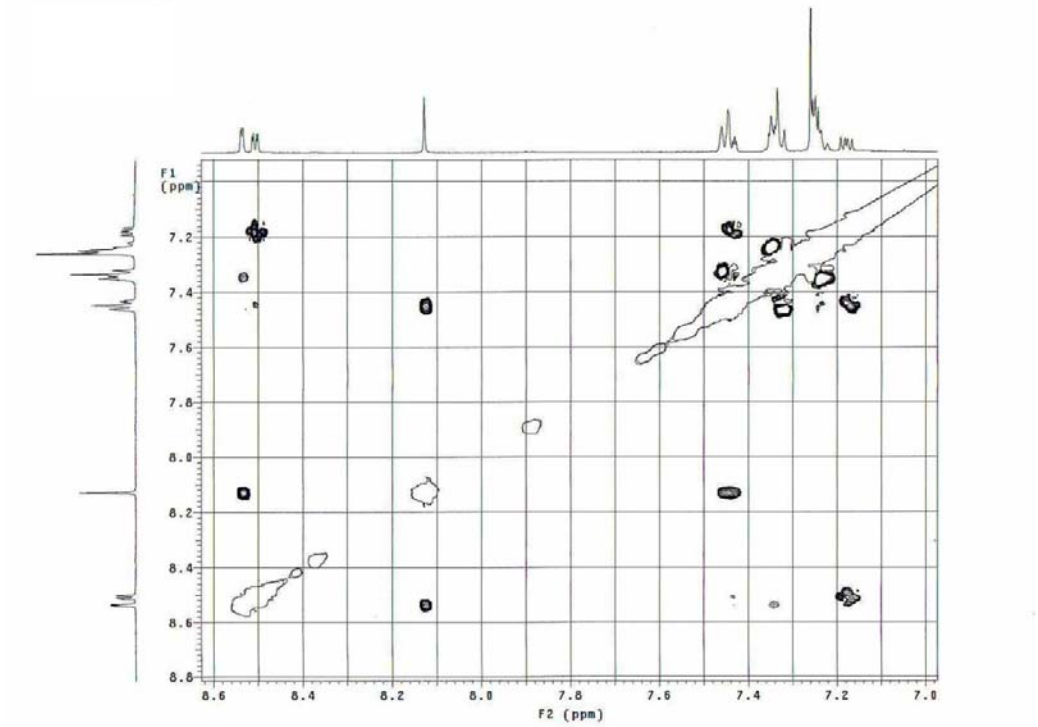
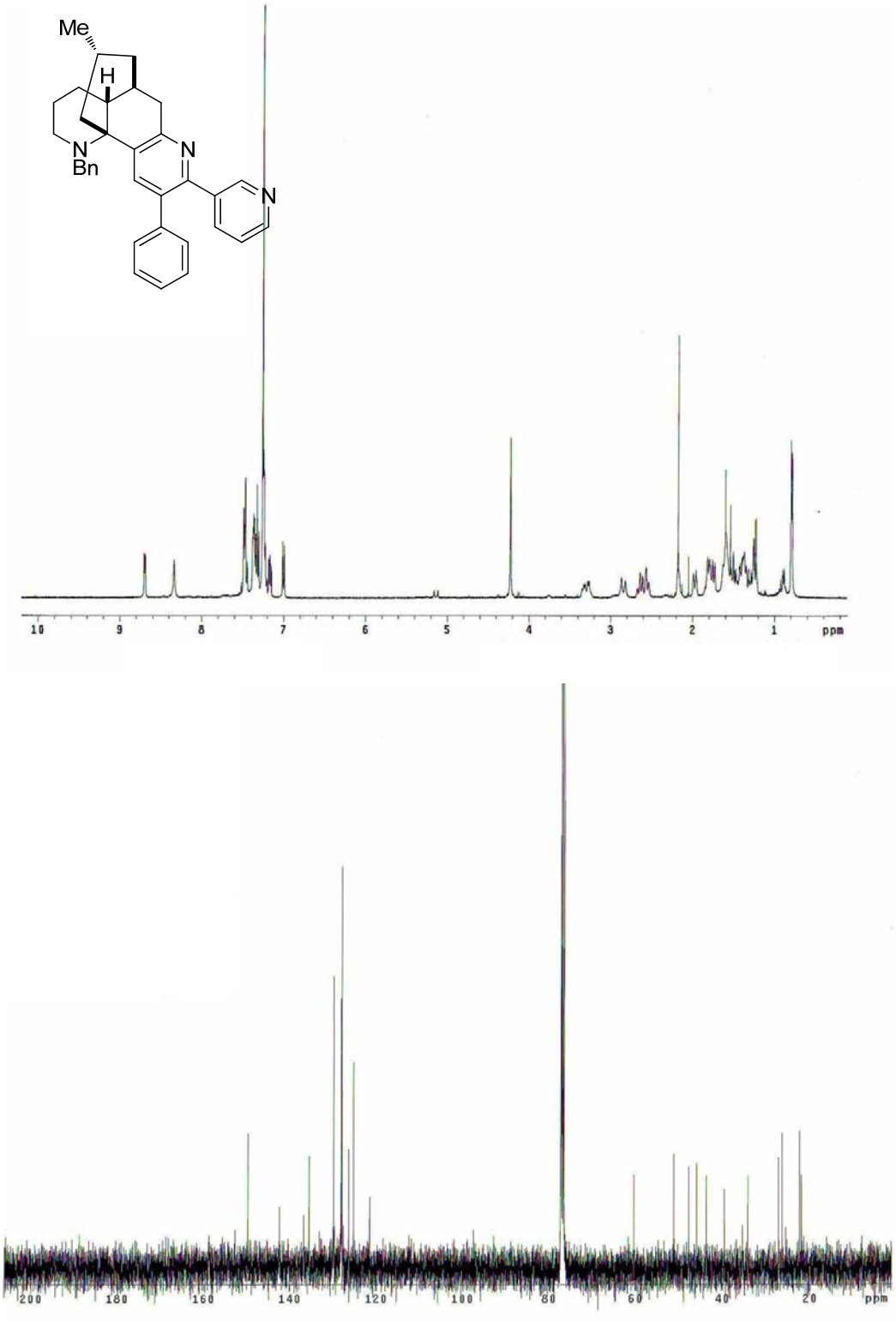

F1
(ppm)
F2 (ppm)


F1
(ppm)
F2 (ppm)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Bn
N
N
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2
1
ppm
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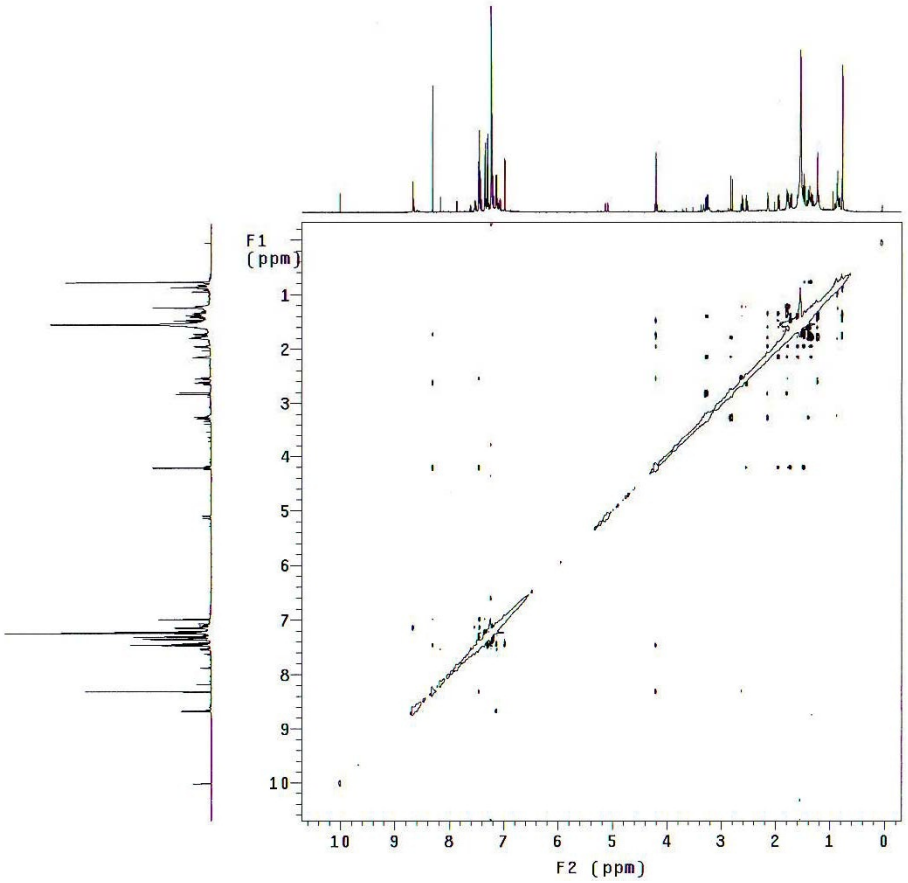
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(ppm)
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3
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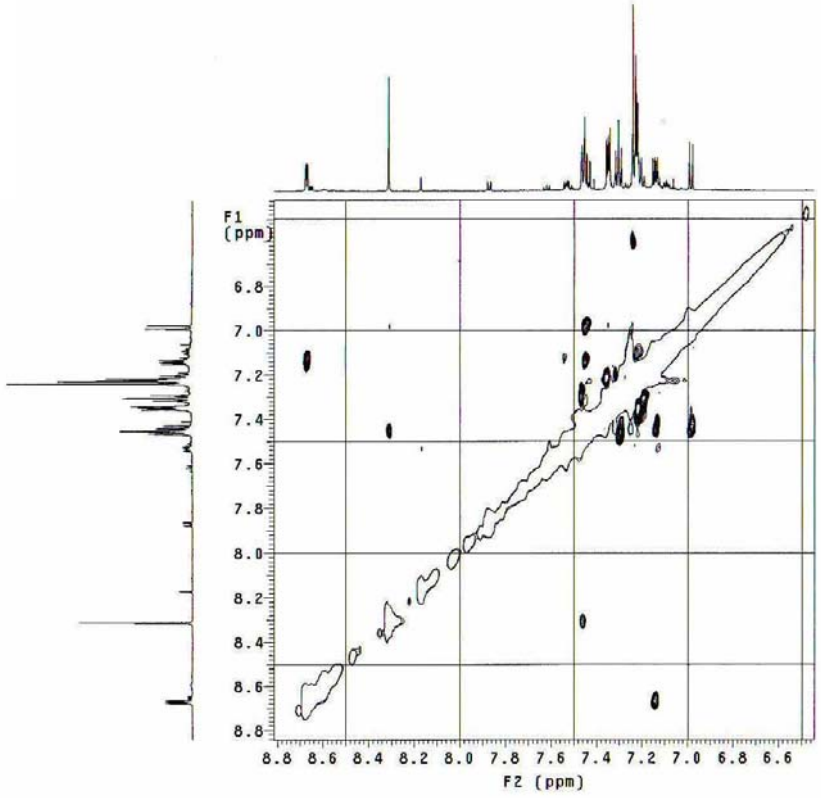
6
7
8
9
10
10 9 8 7 6 5 4 3 2 1 0
F2 (ppm)


F1
(ppm)
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7.0
7.2
7.4
7.6
7.8
8.0
8.2
8.4
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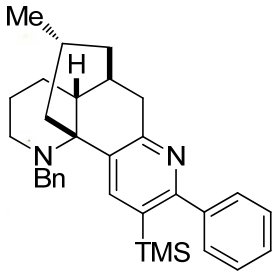
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6
F2 (ppm)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Bn
N
TMS

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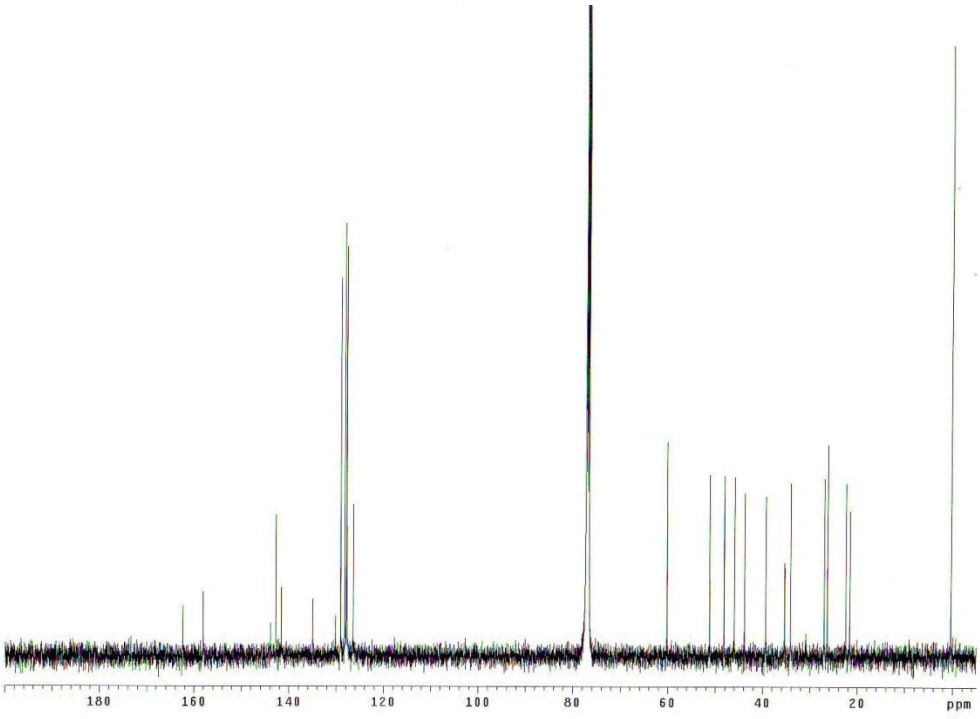
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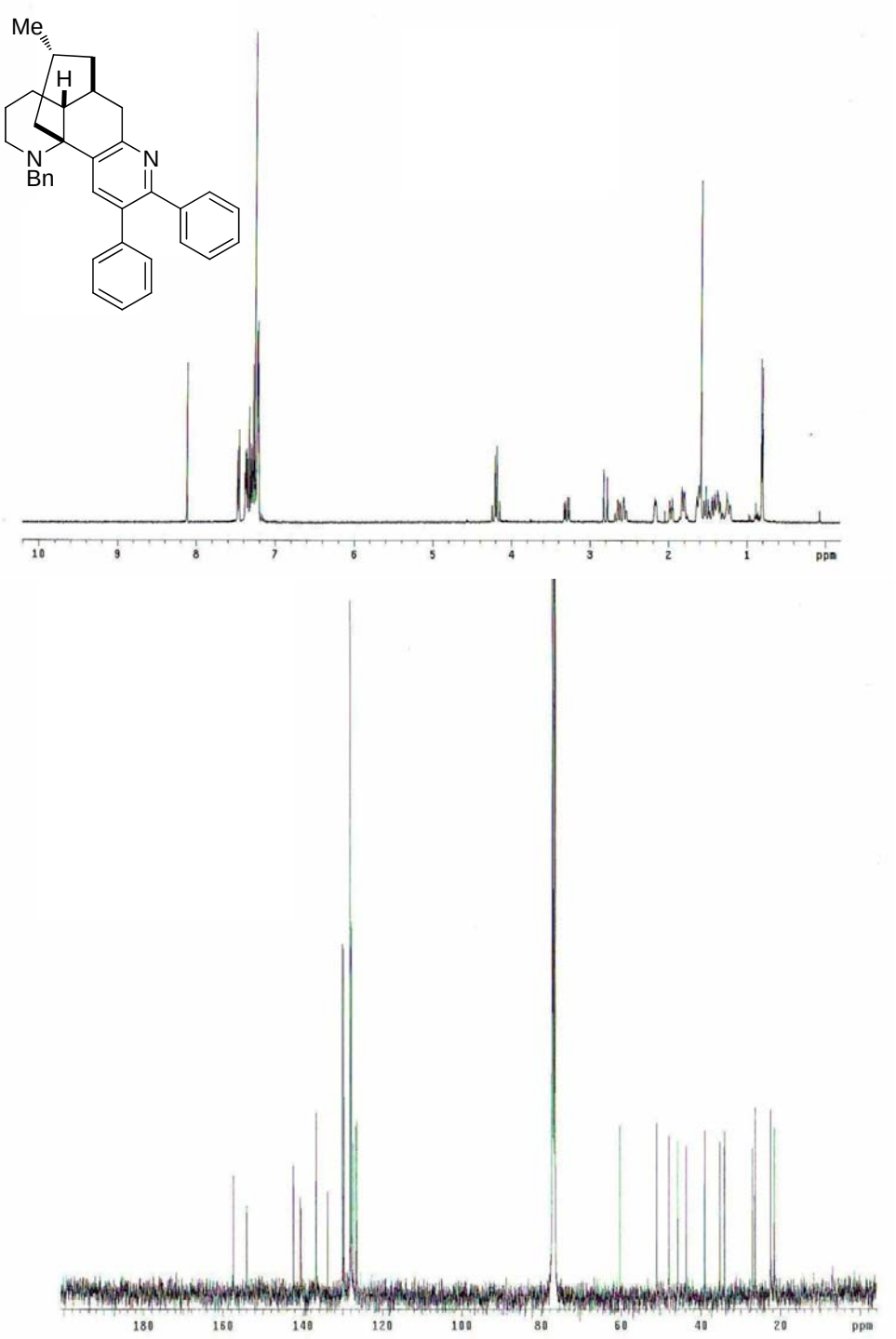
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Bn
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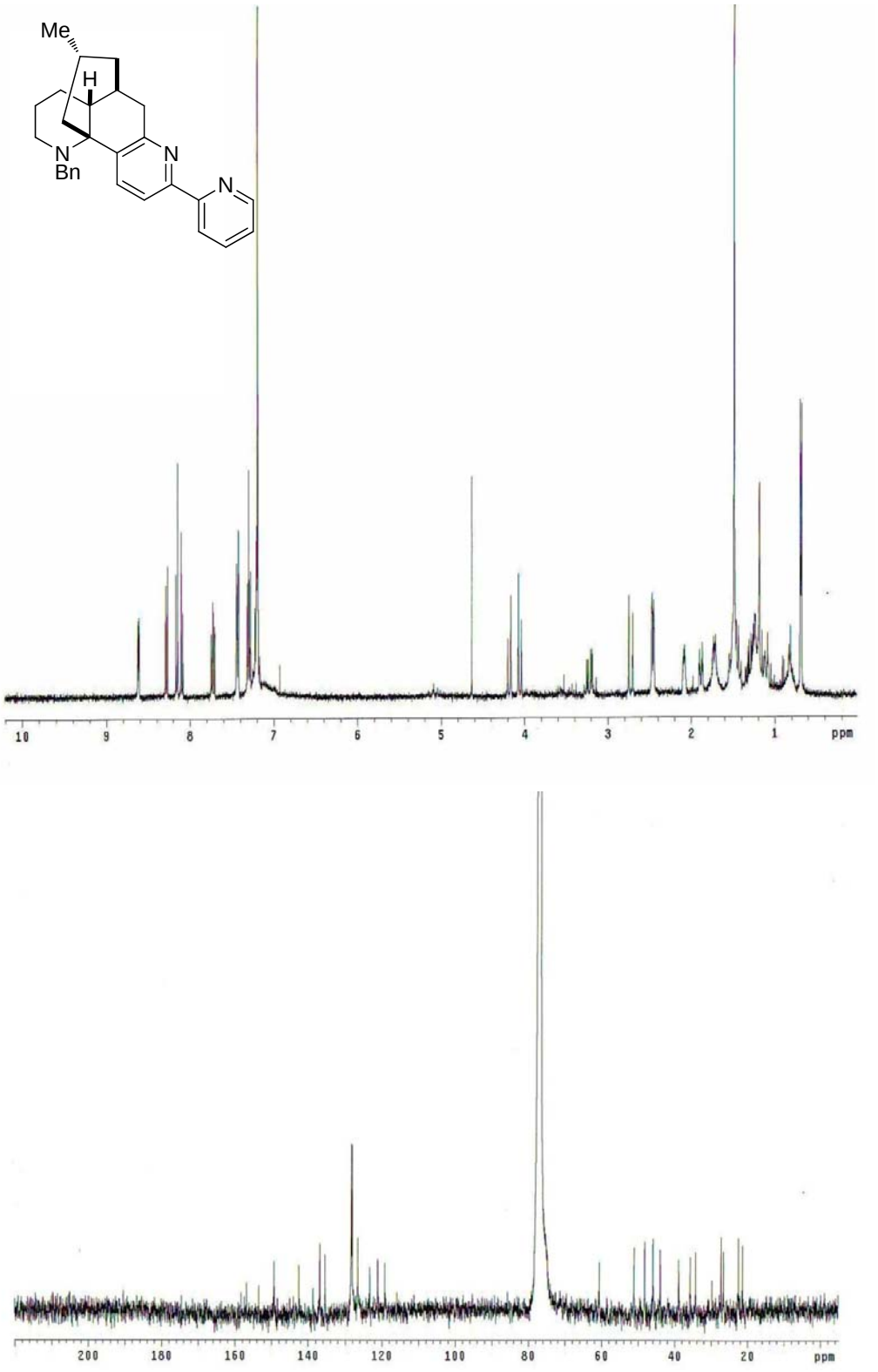
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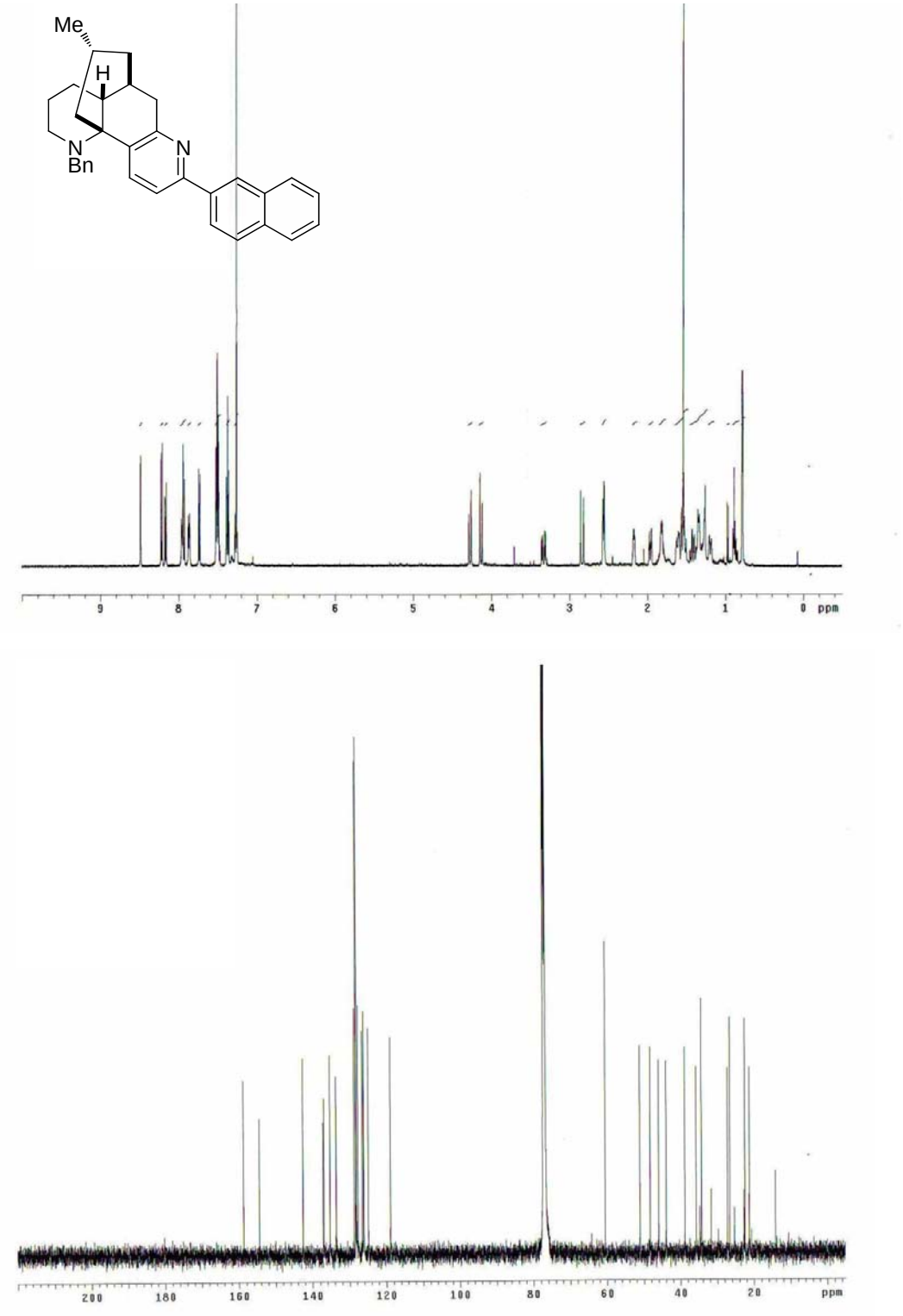
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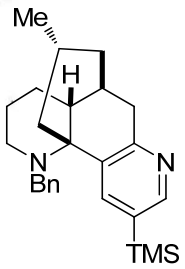
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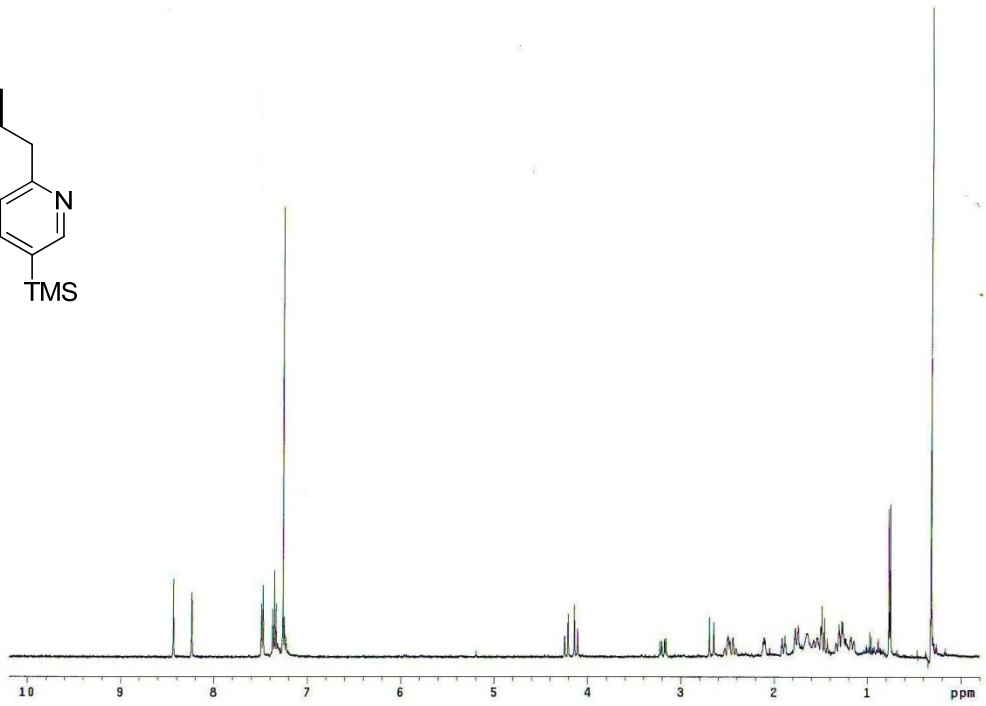
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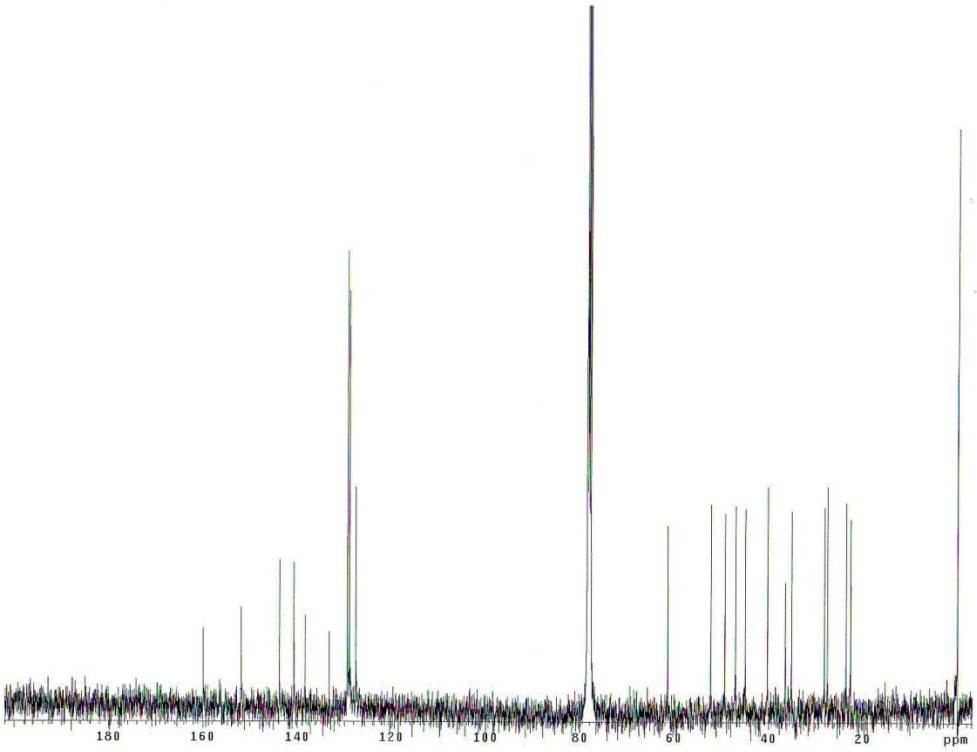
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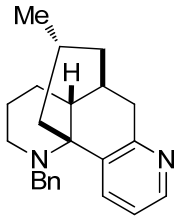
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N

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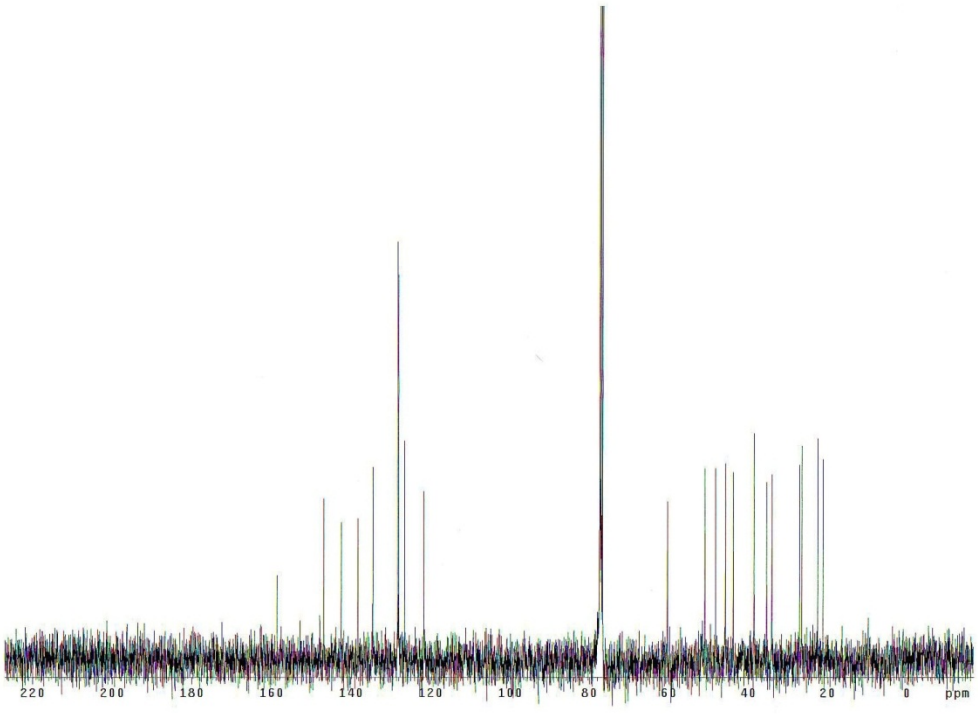
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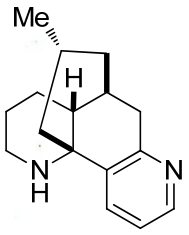
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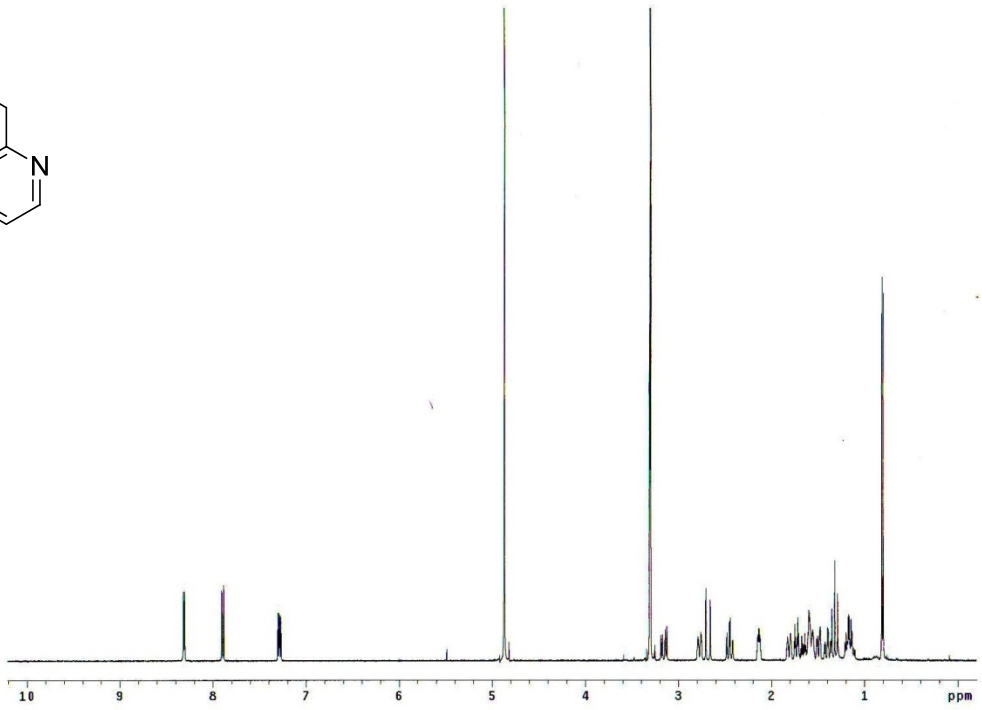
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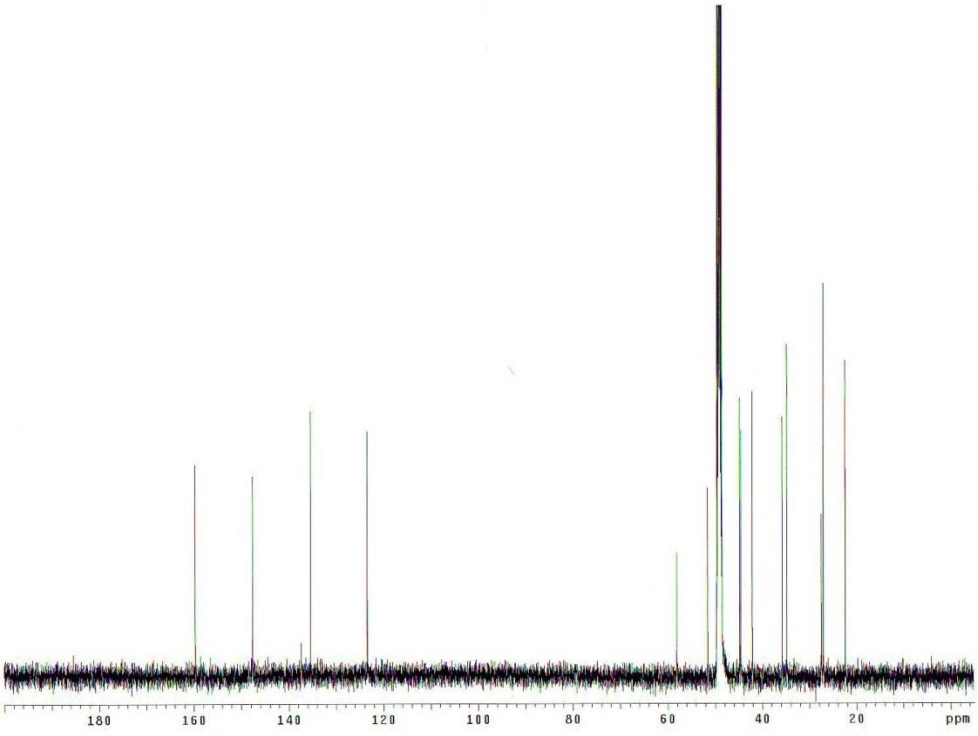
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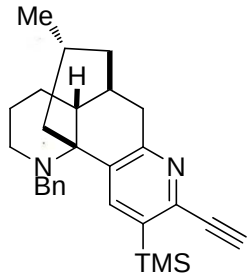
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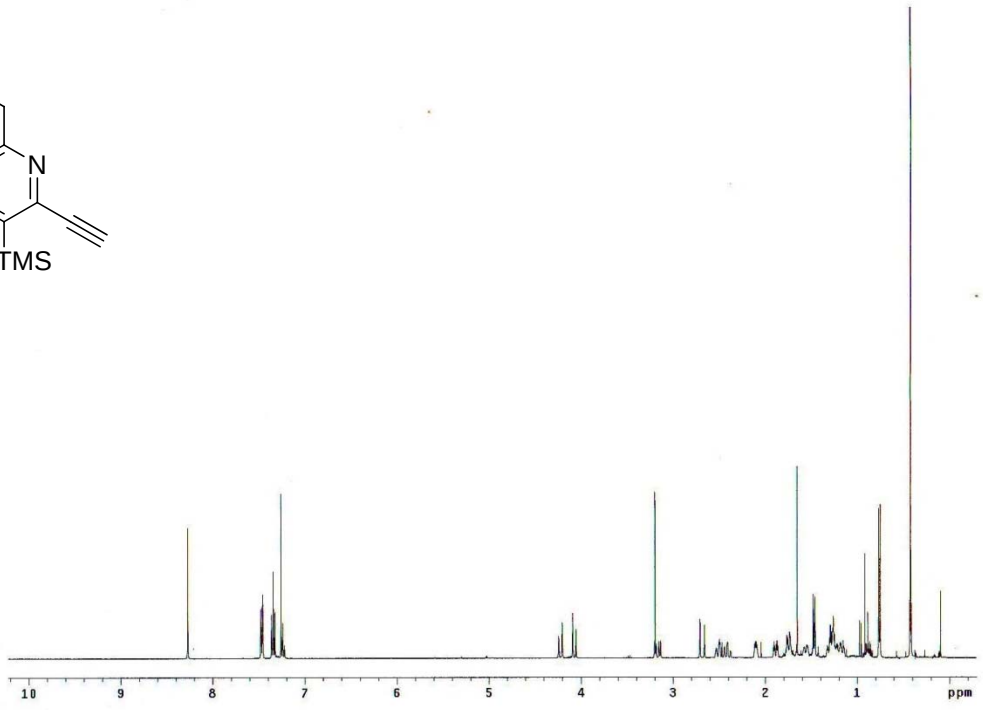
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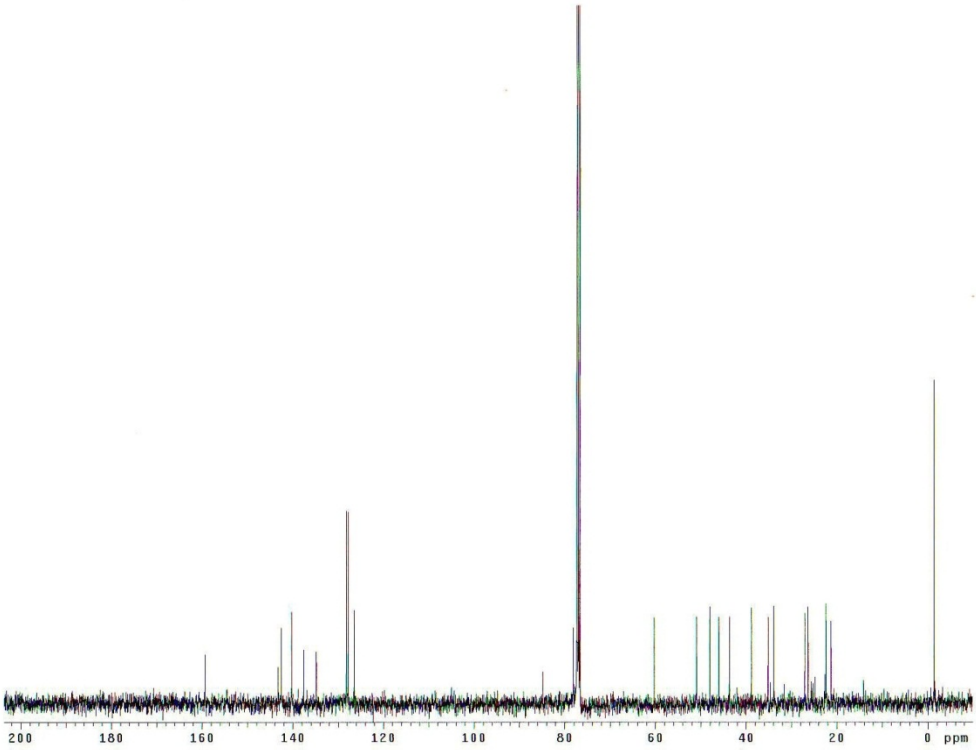
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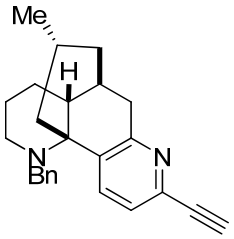
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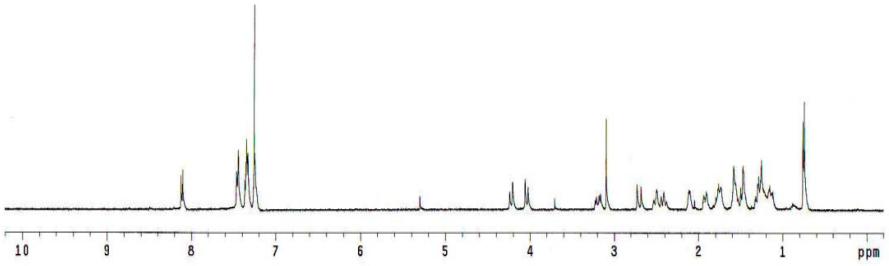
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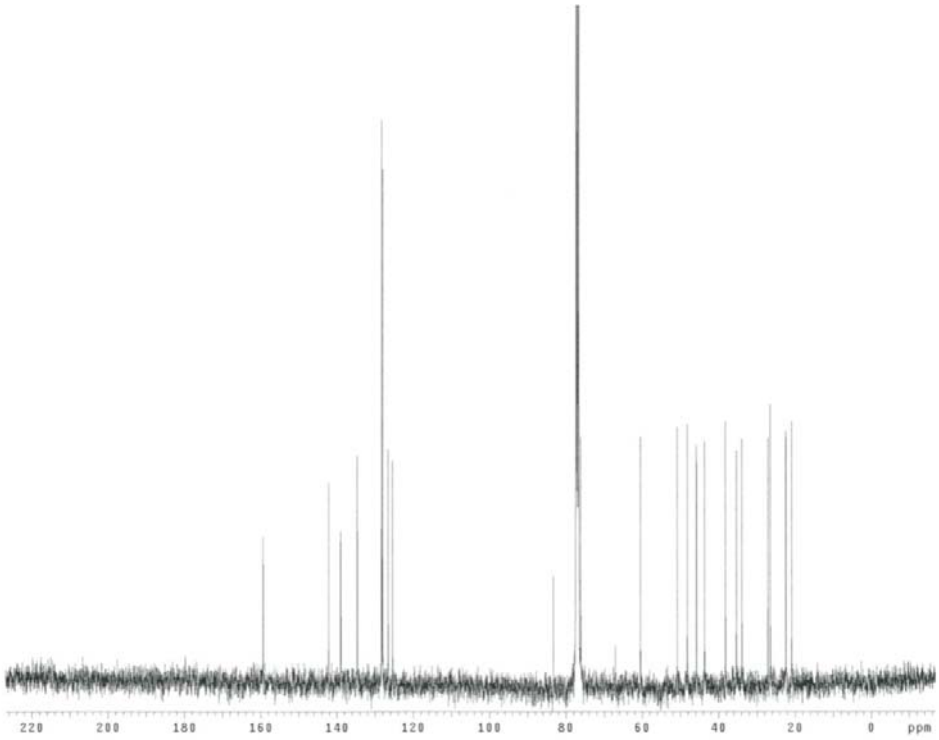
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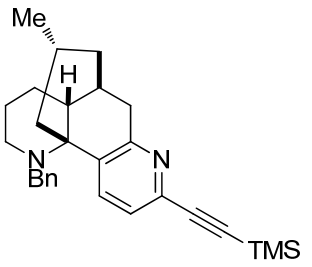
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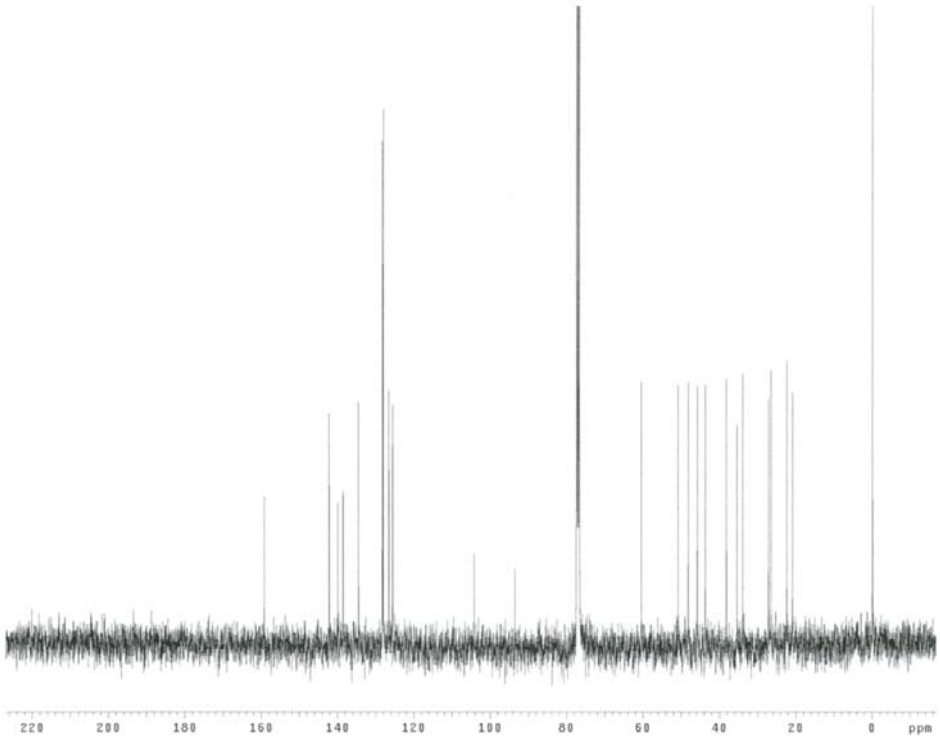
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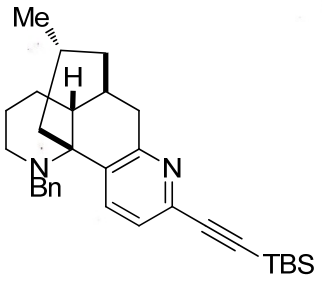
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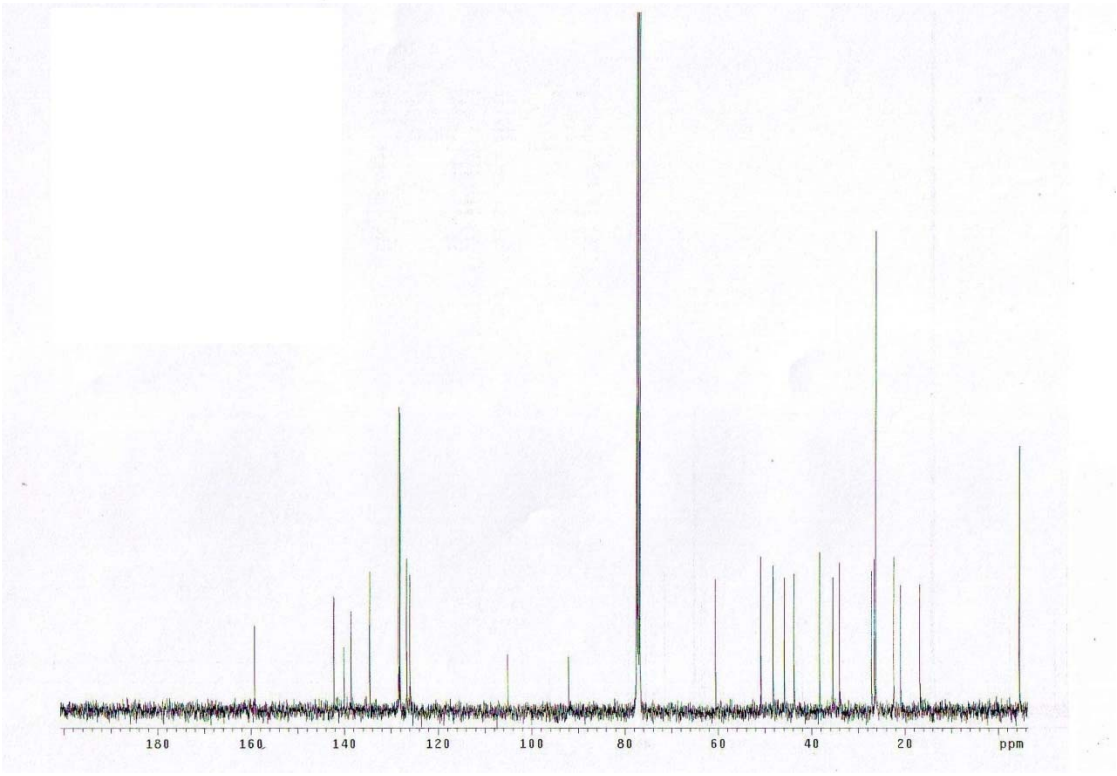
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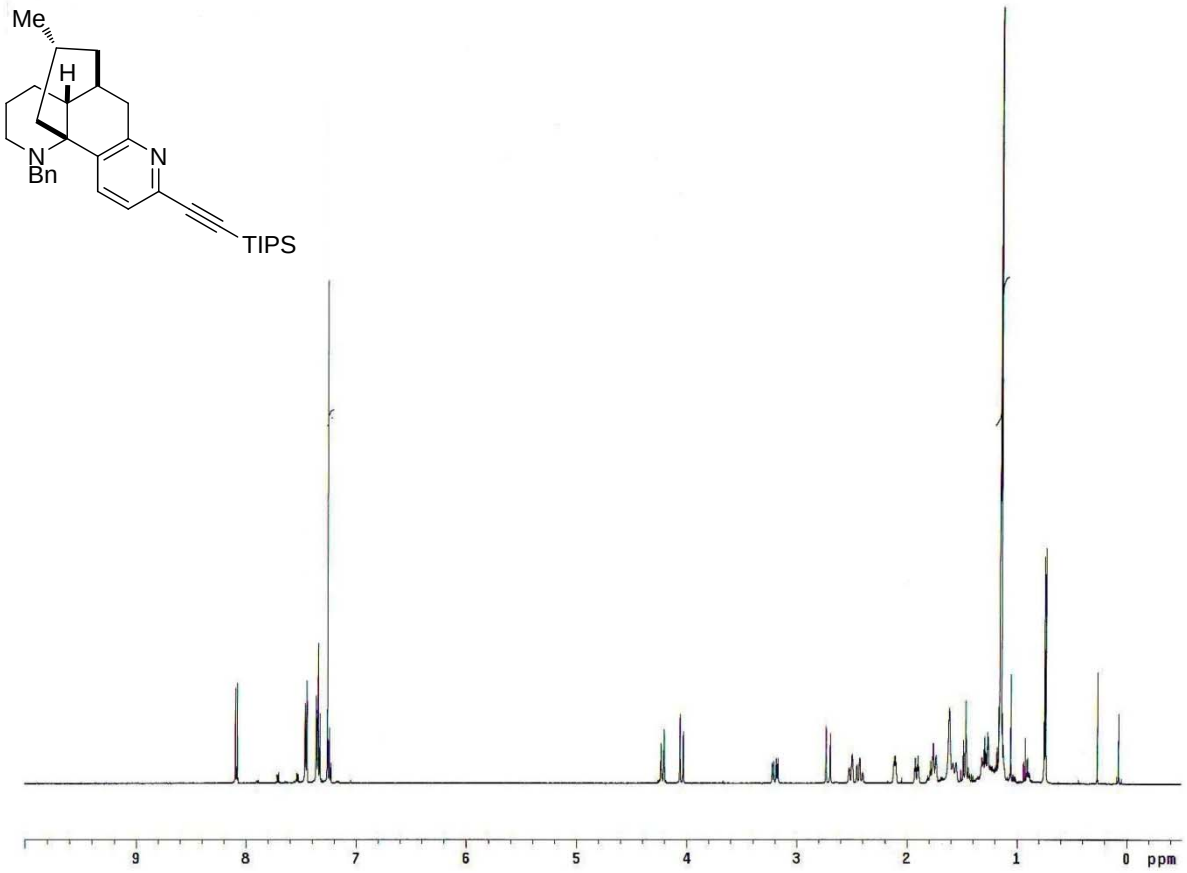
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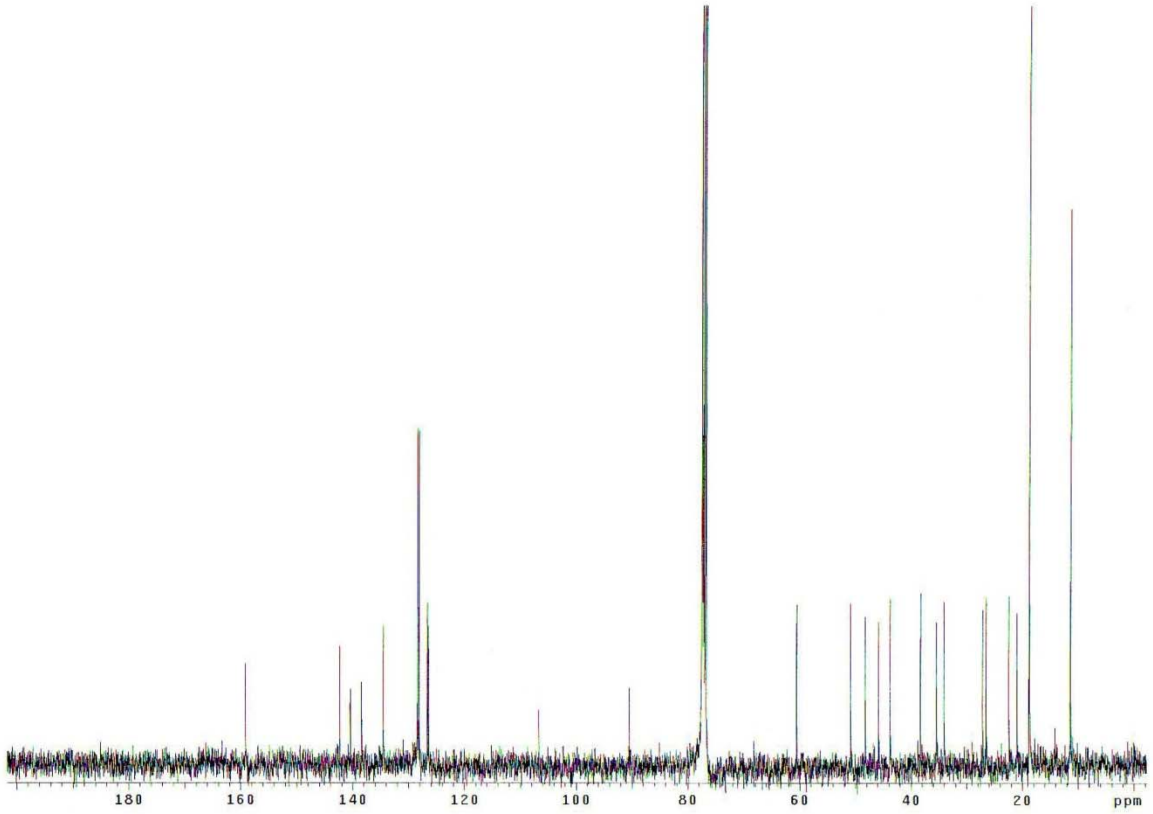
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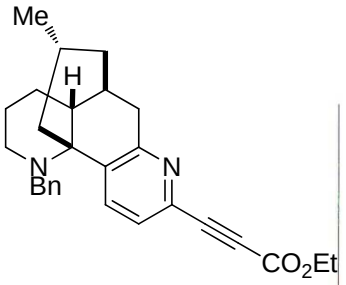
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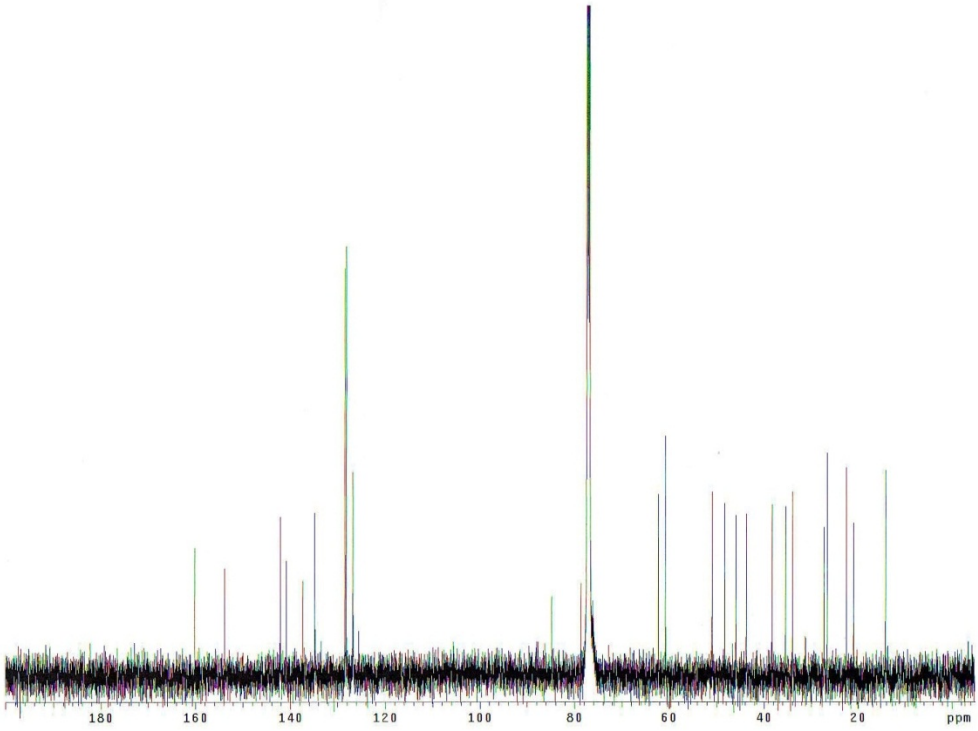
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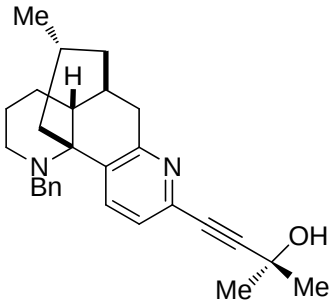
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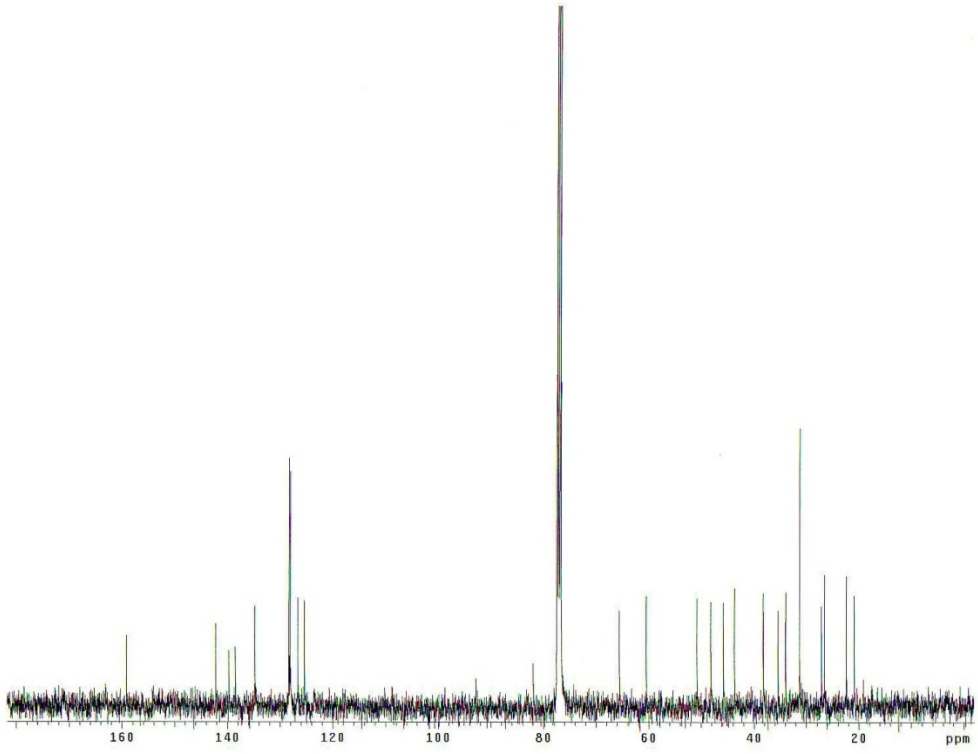
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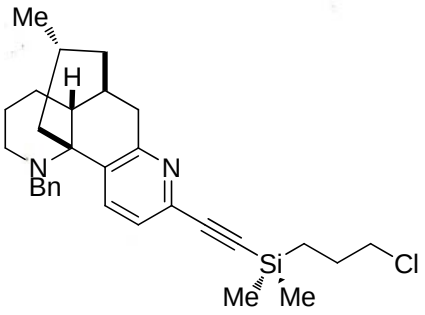
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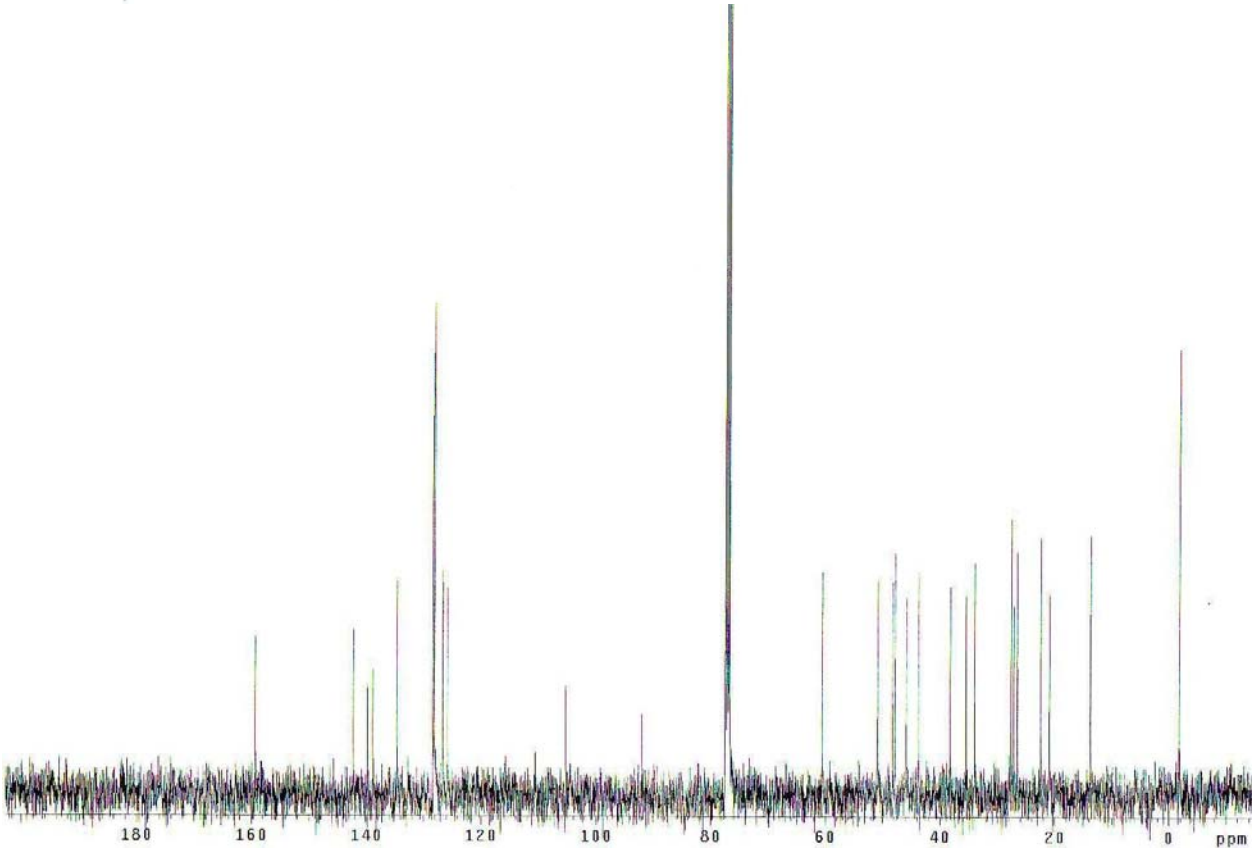
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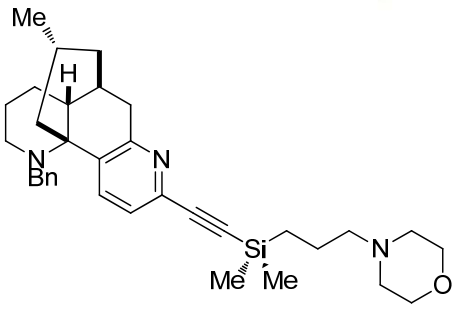
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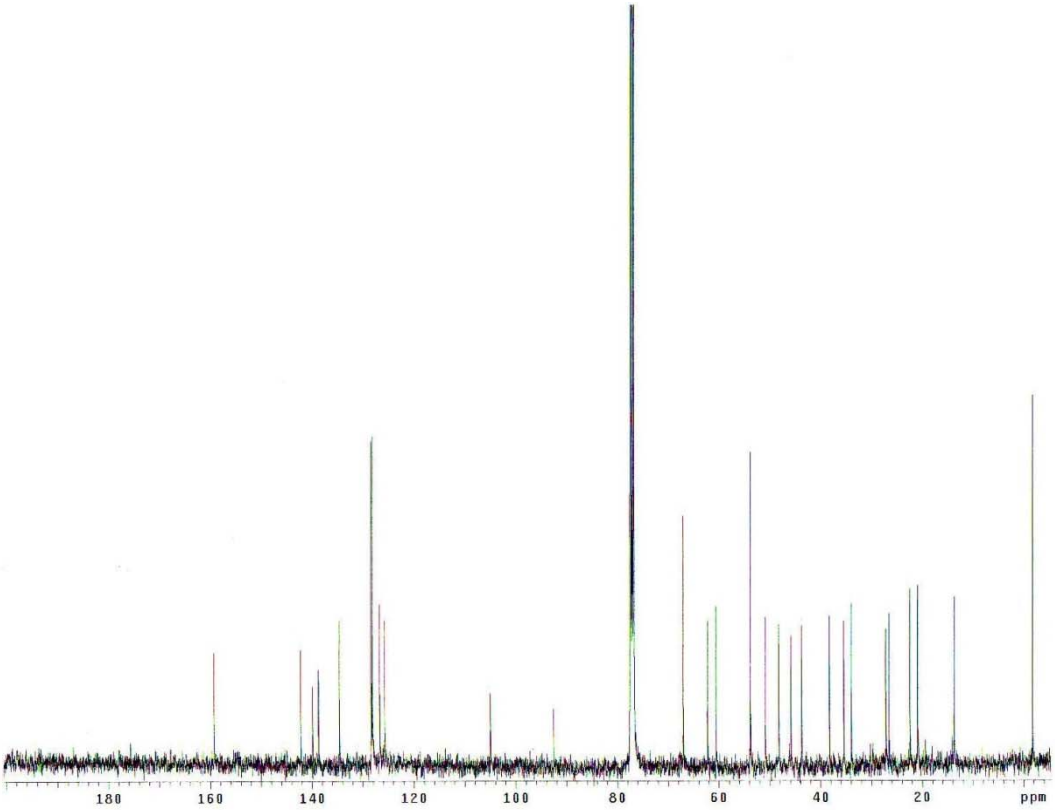
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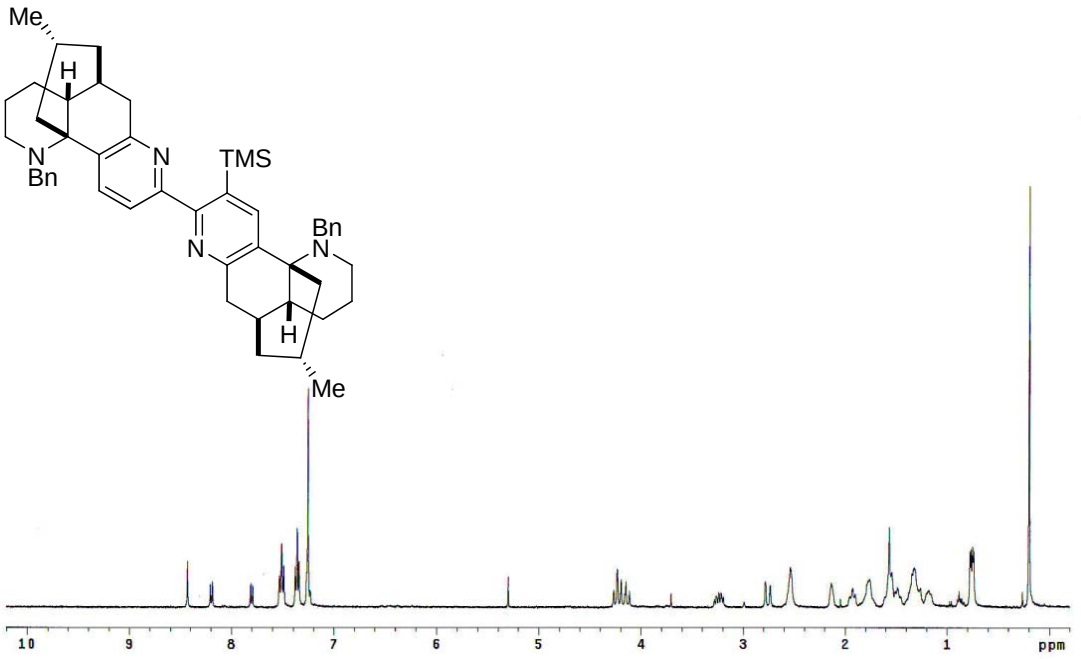
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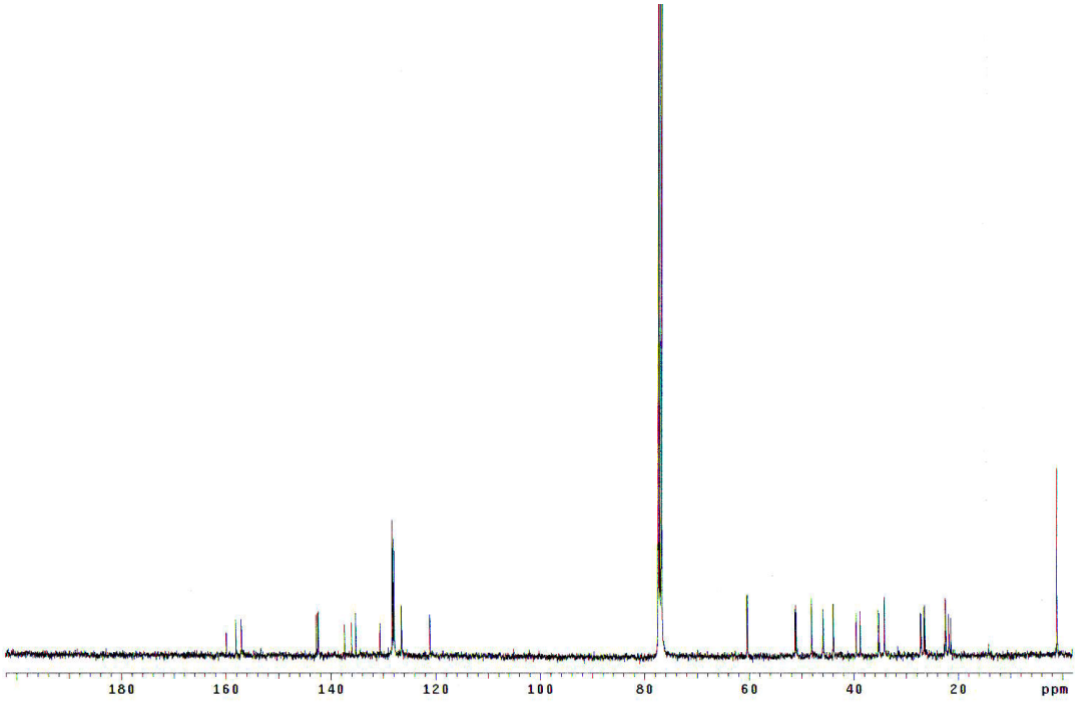
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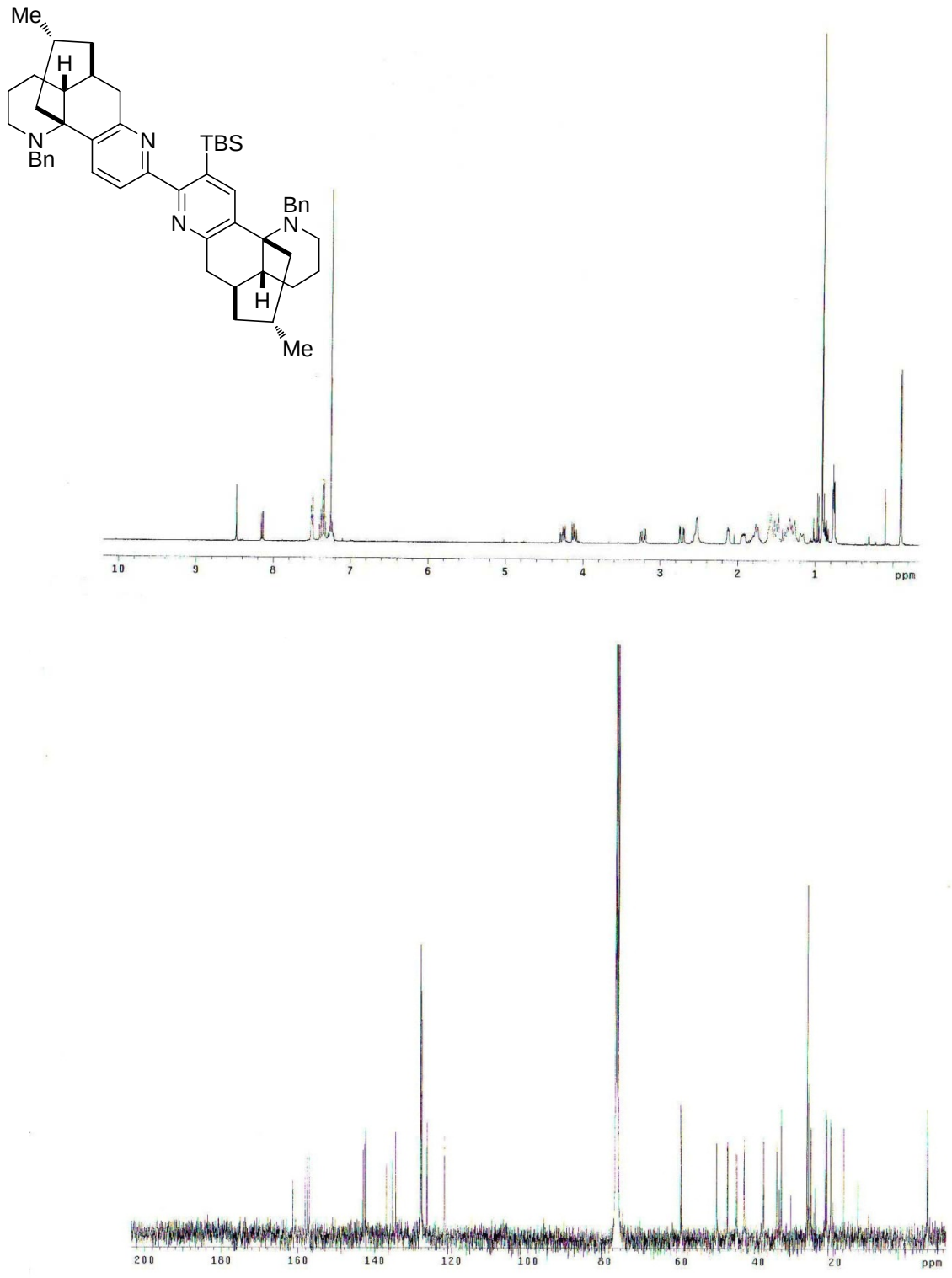
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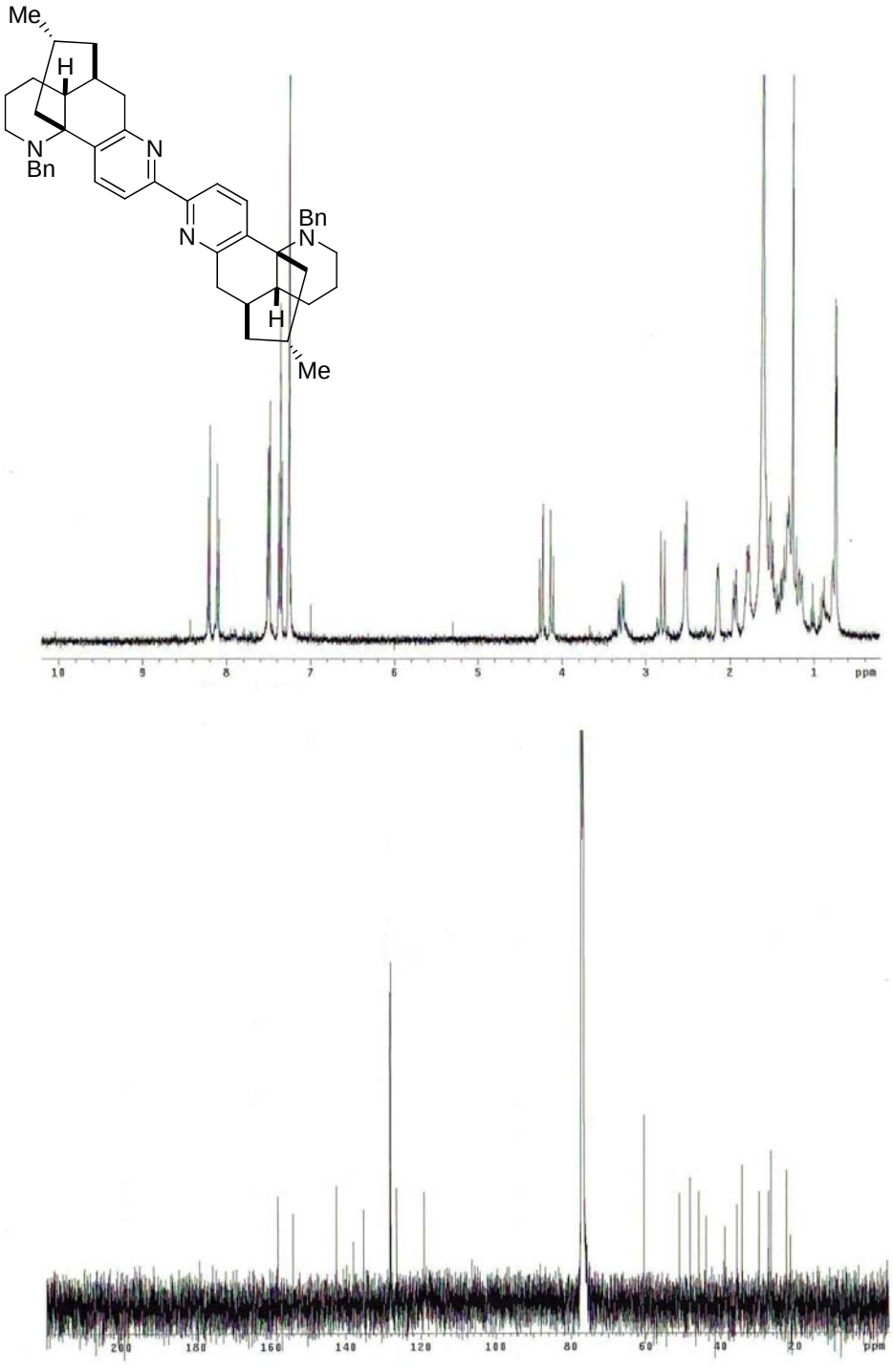
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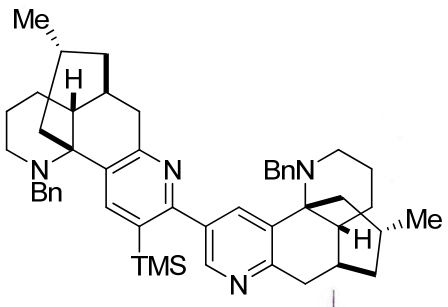
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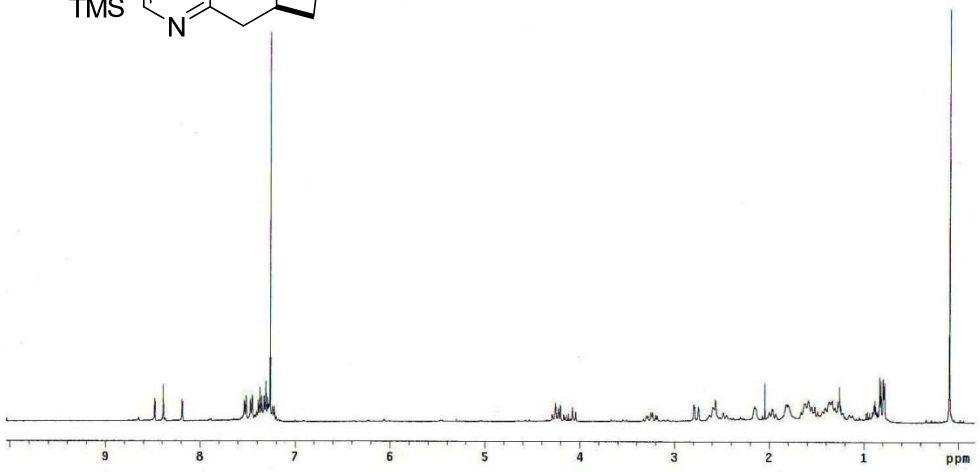
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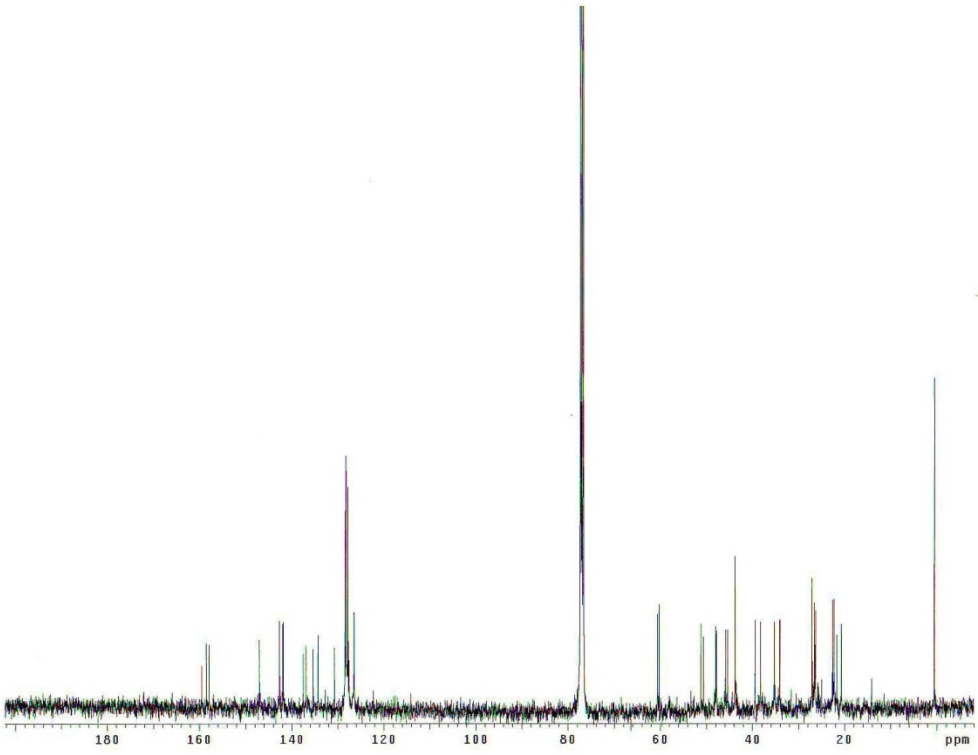
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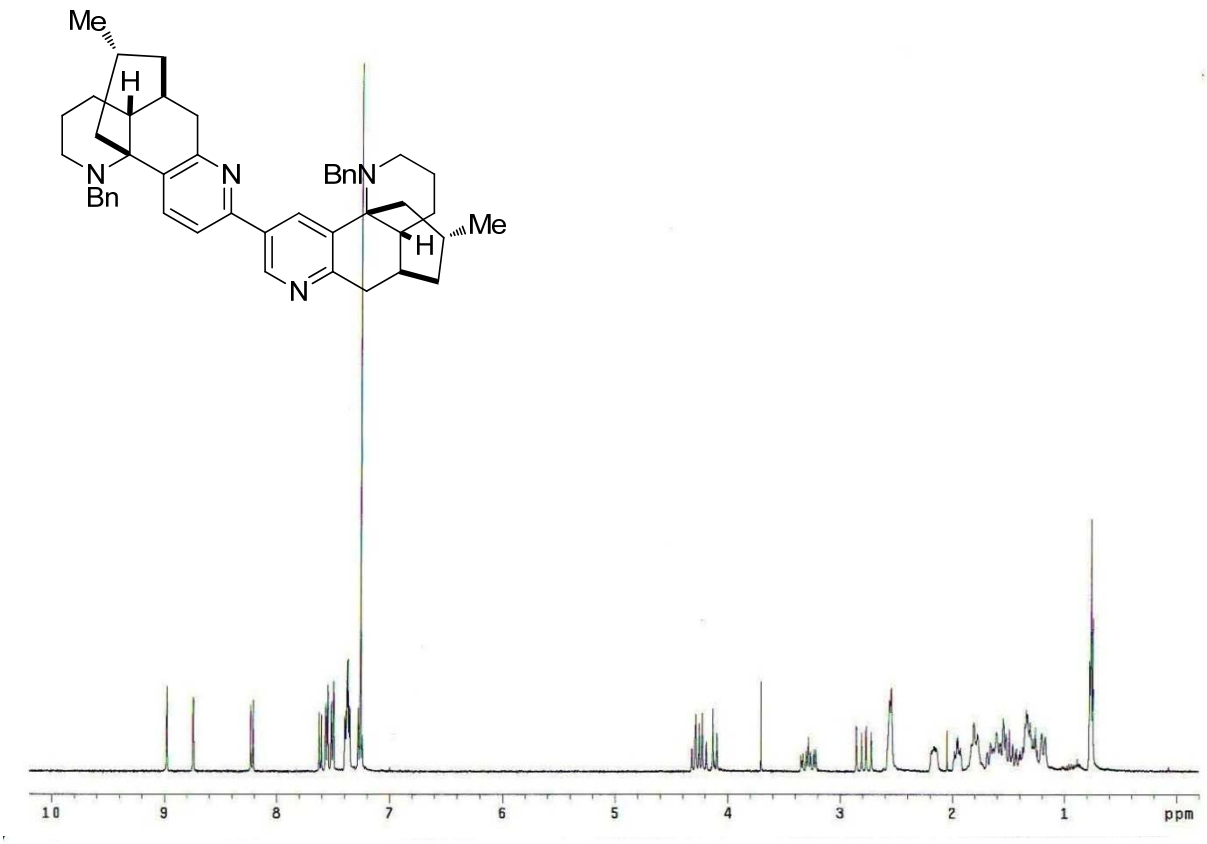
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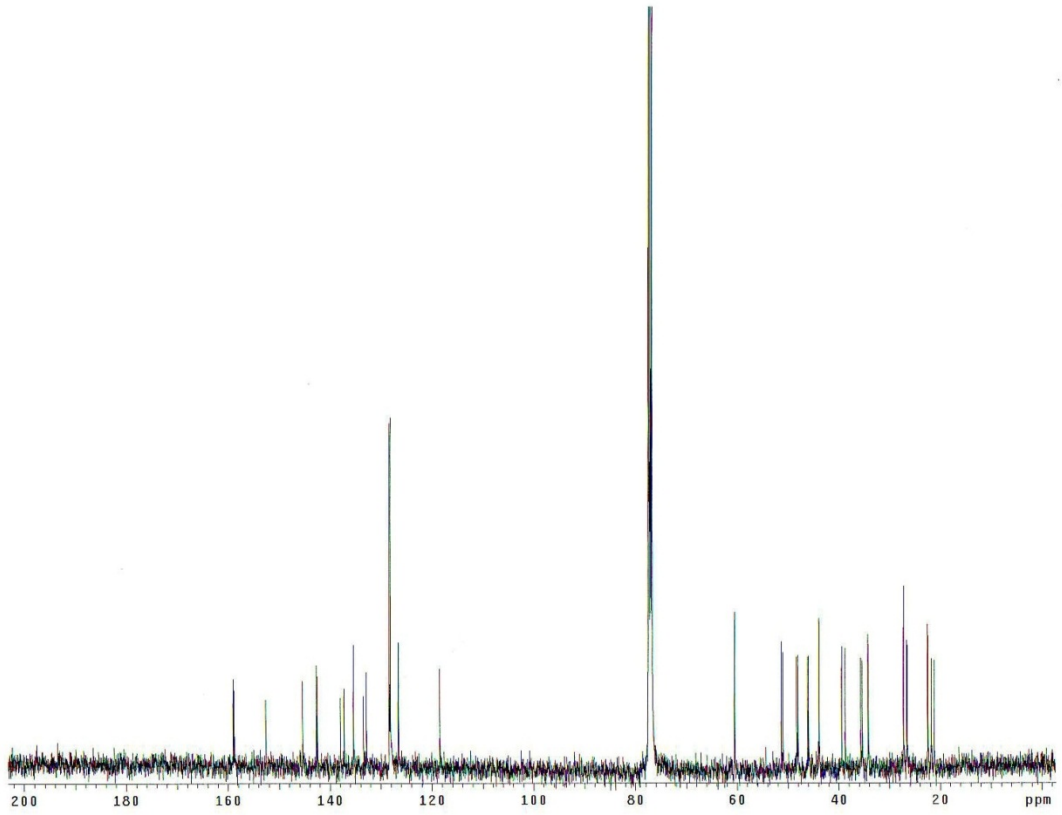
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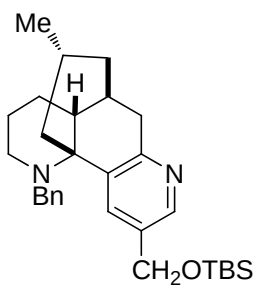
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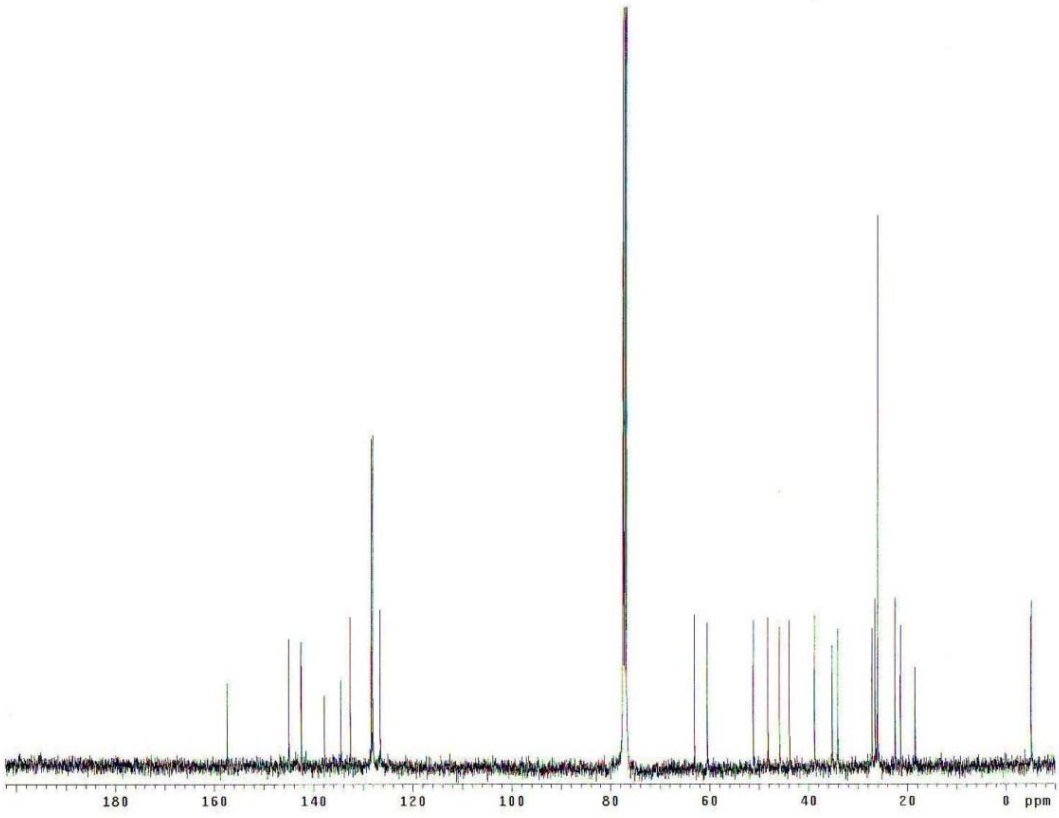
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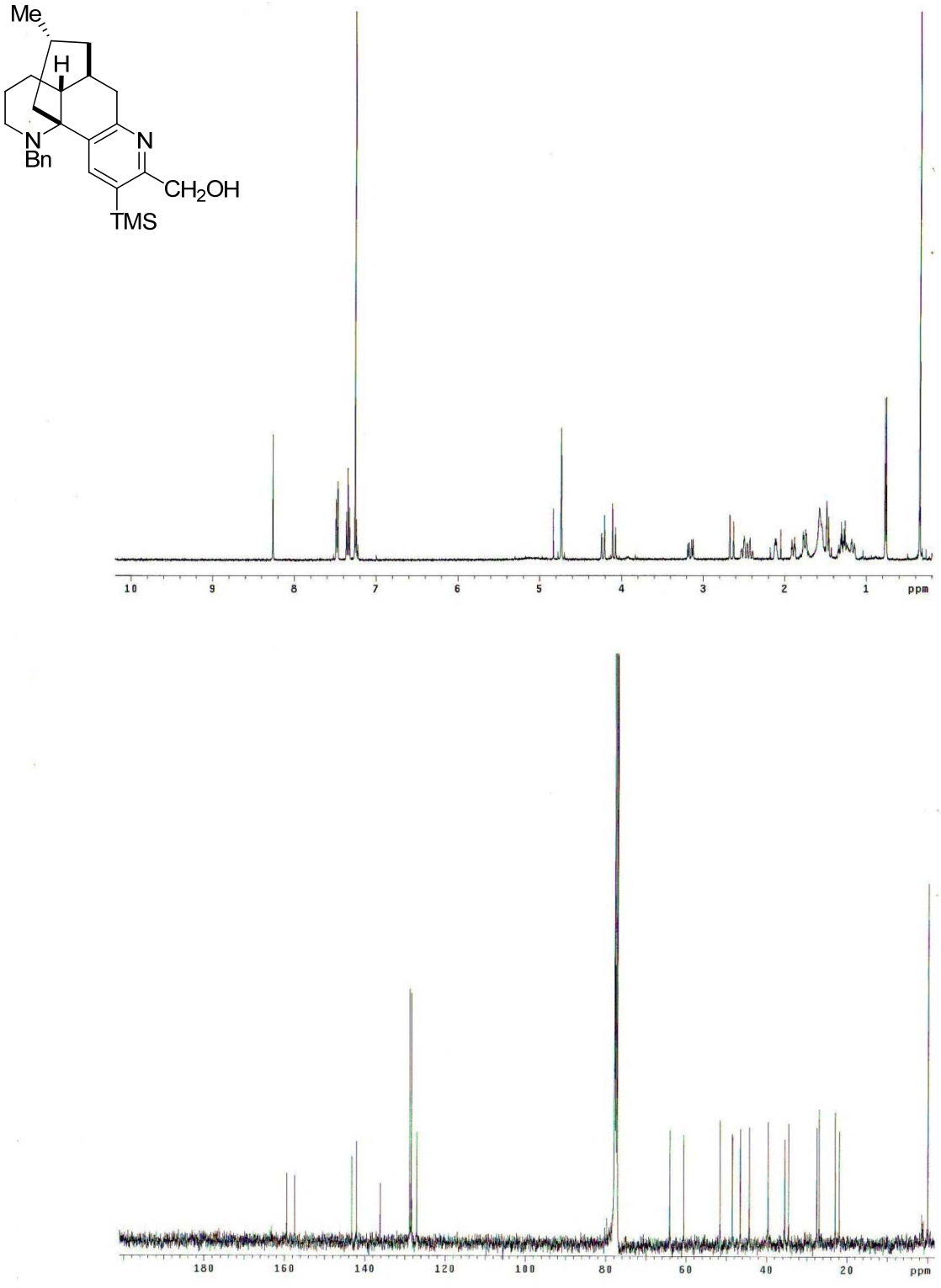
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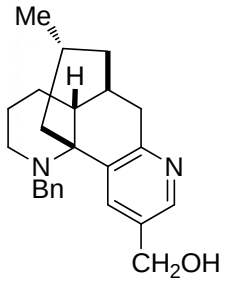
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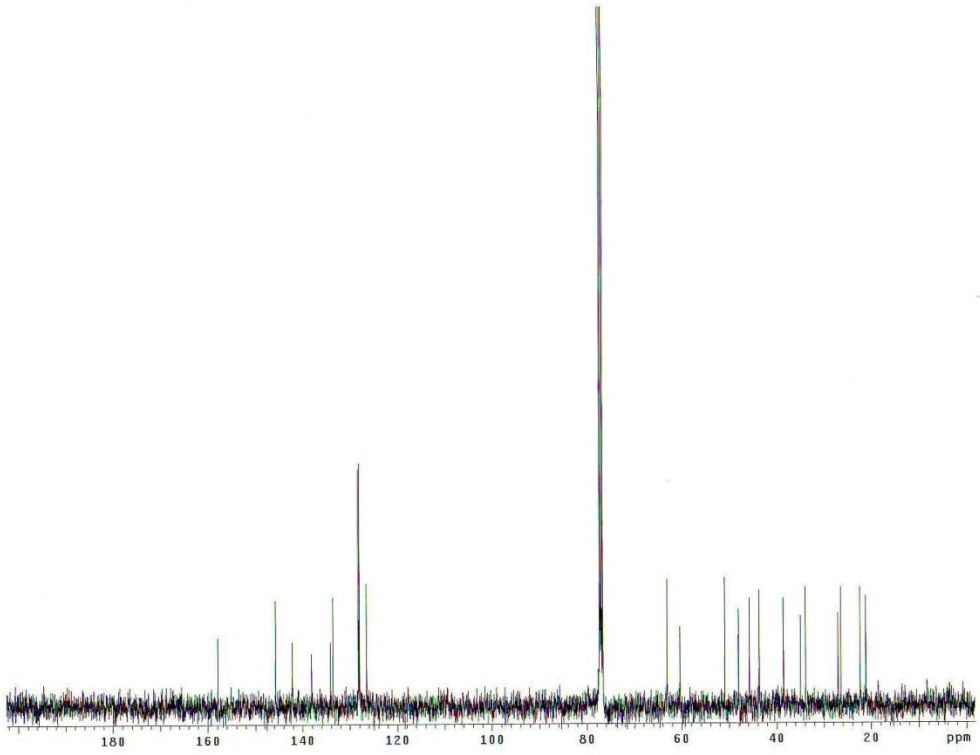
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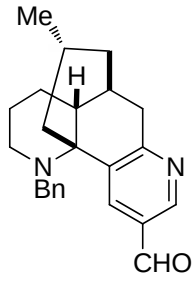
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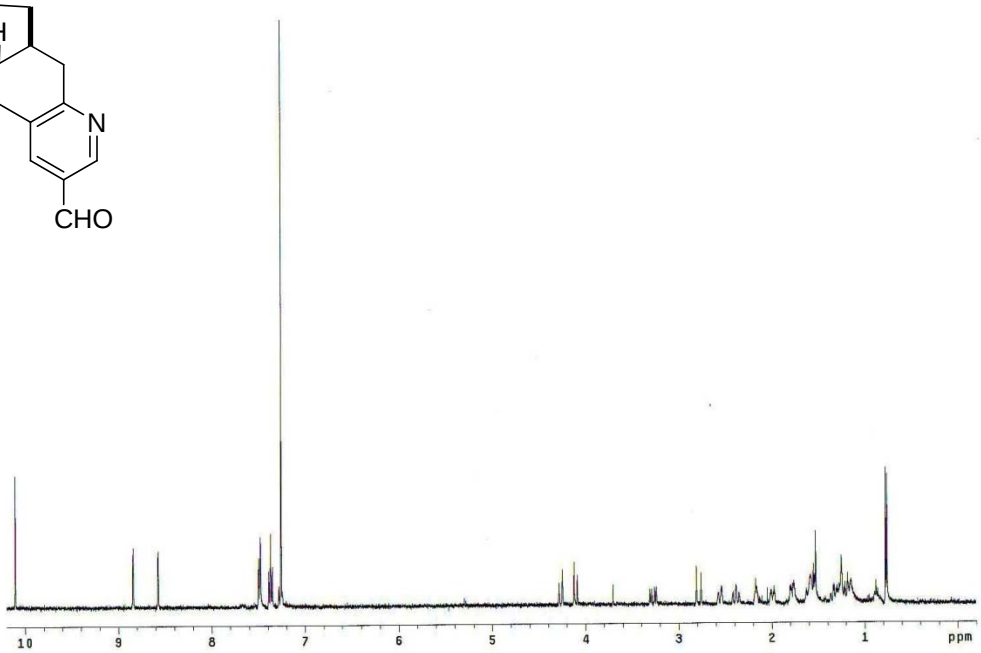
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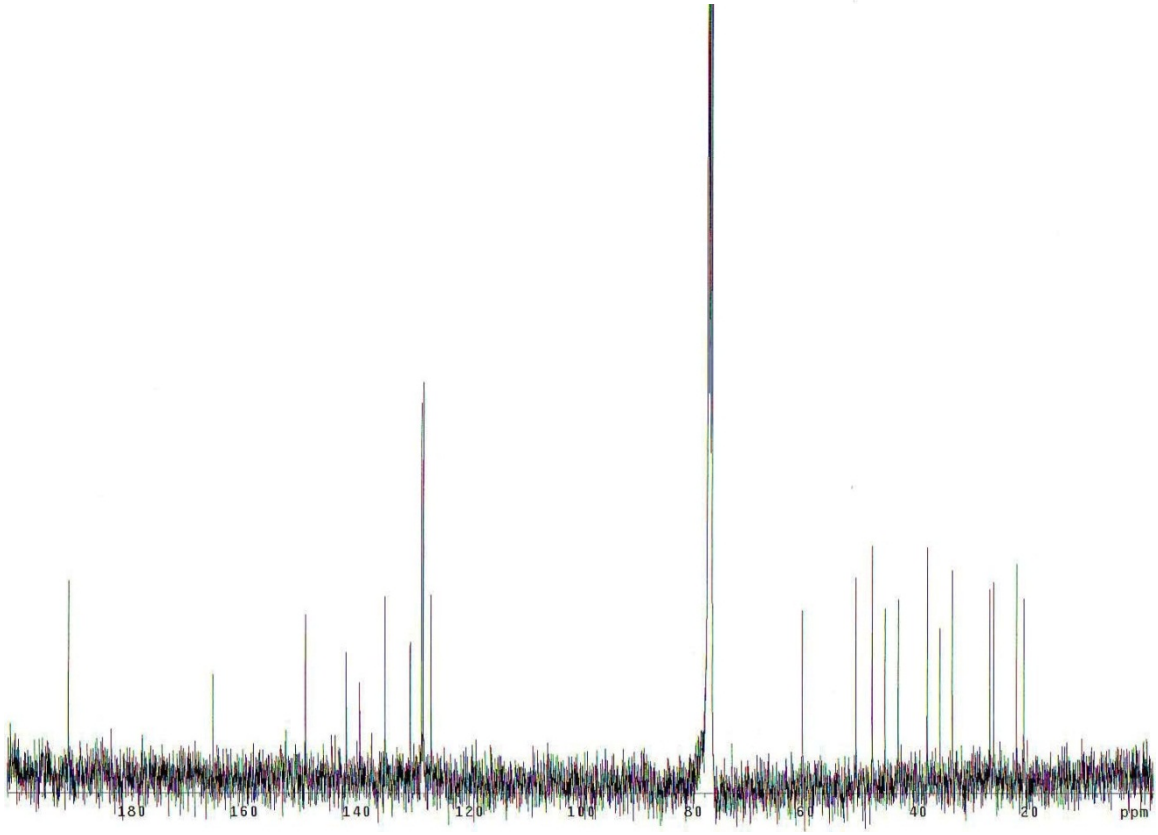
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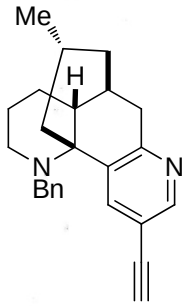
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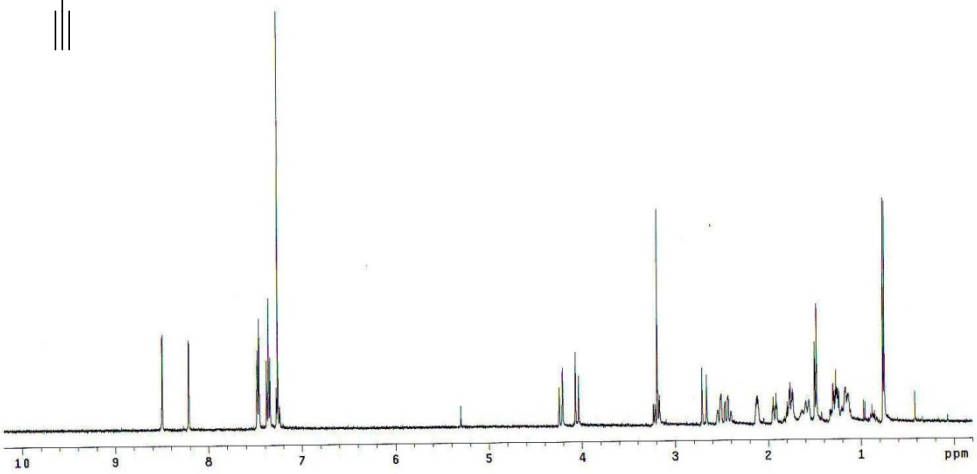
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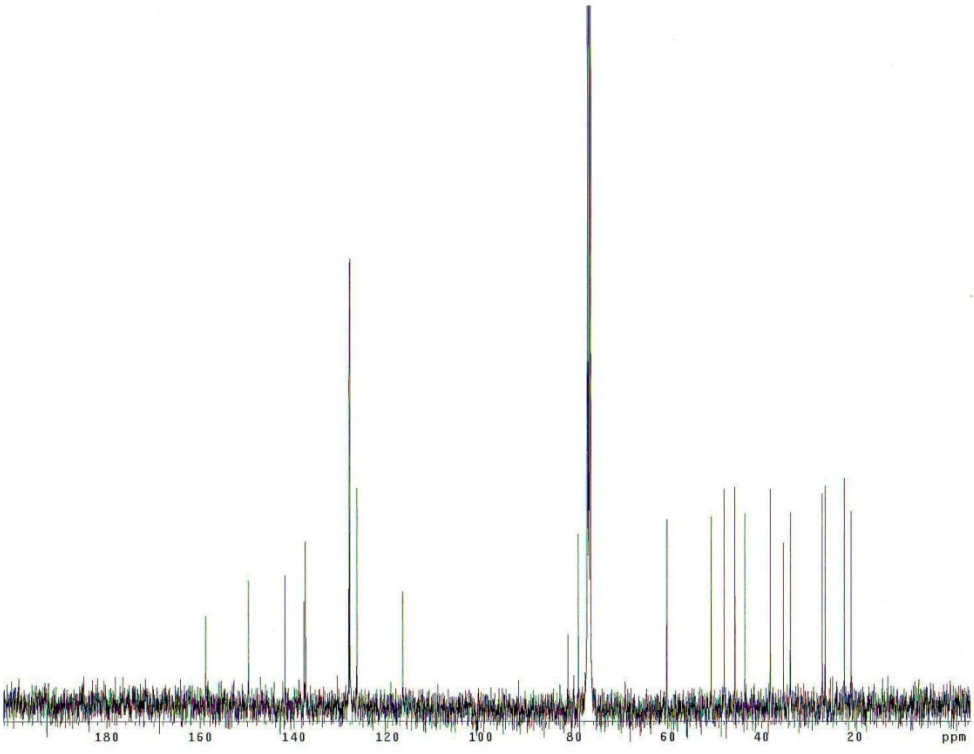
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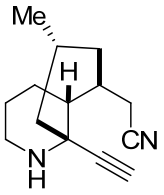
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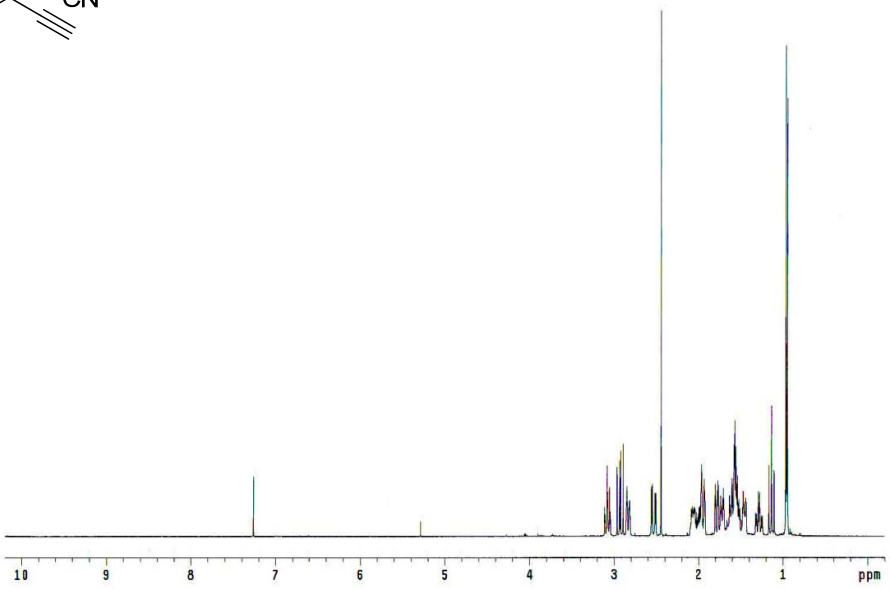
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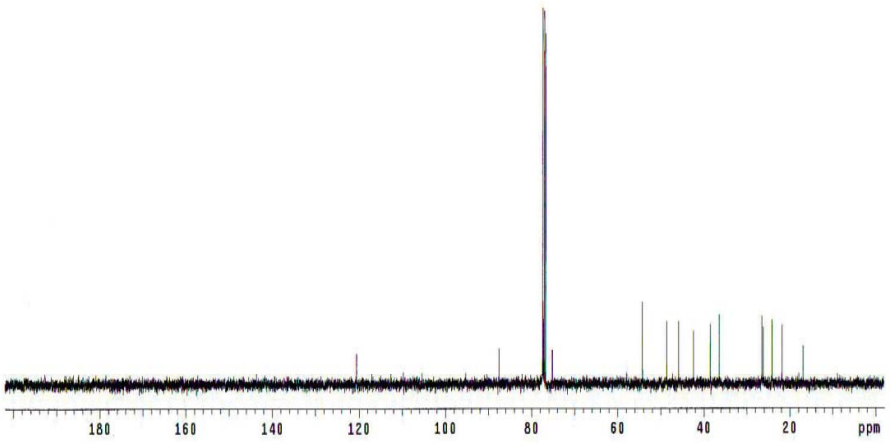
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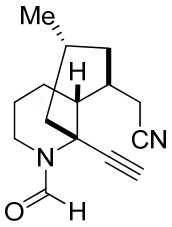
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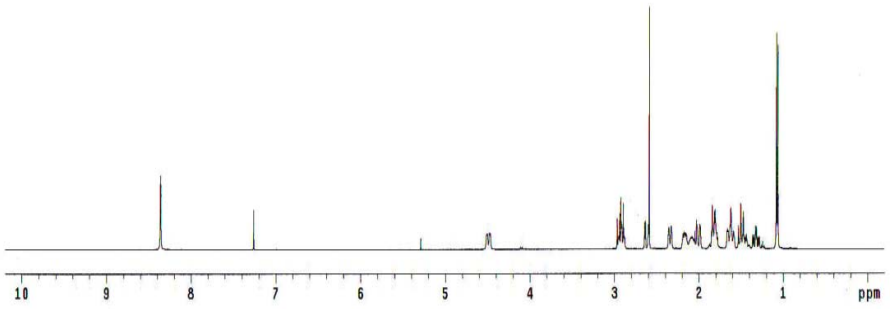
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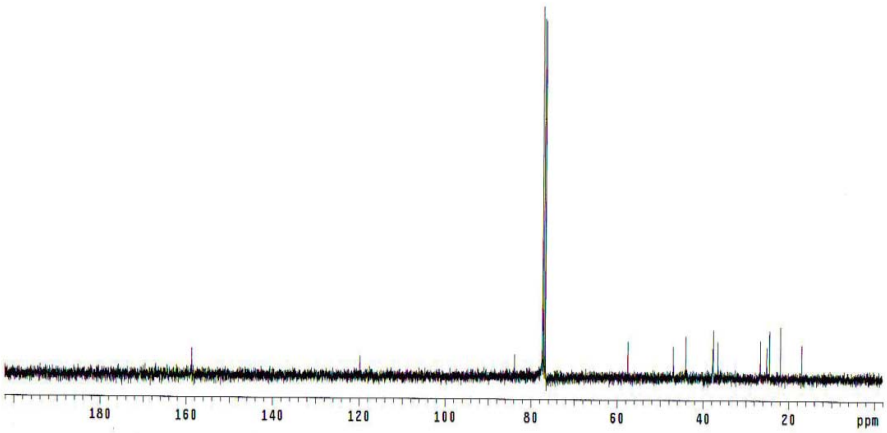
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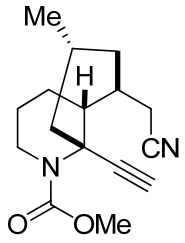
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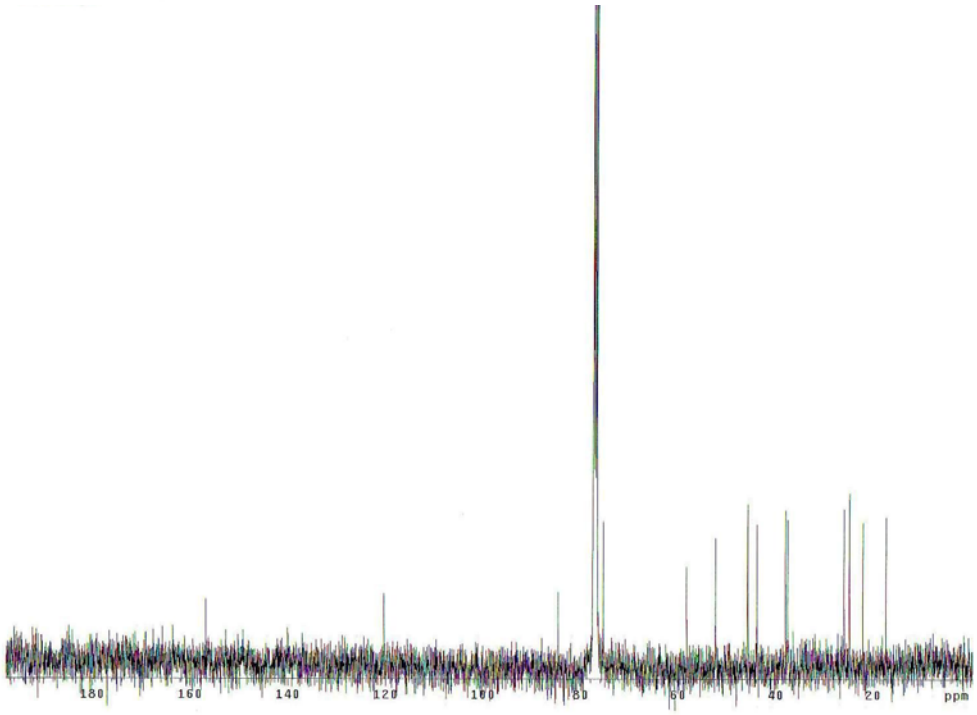
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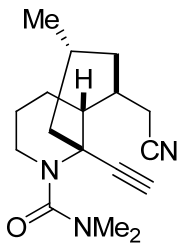
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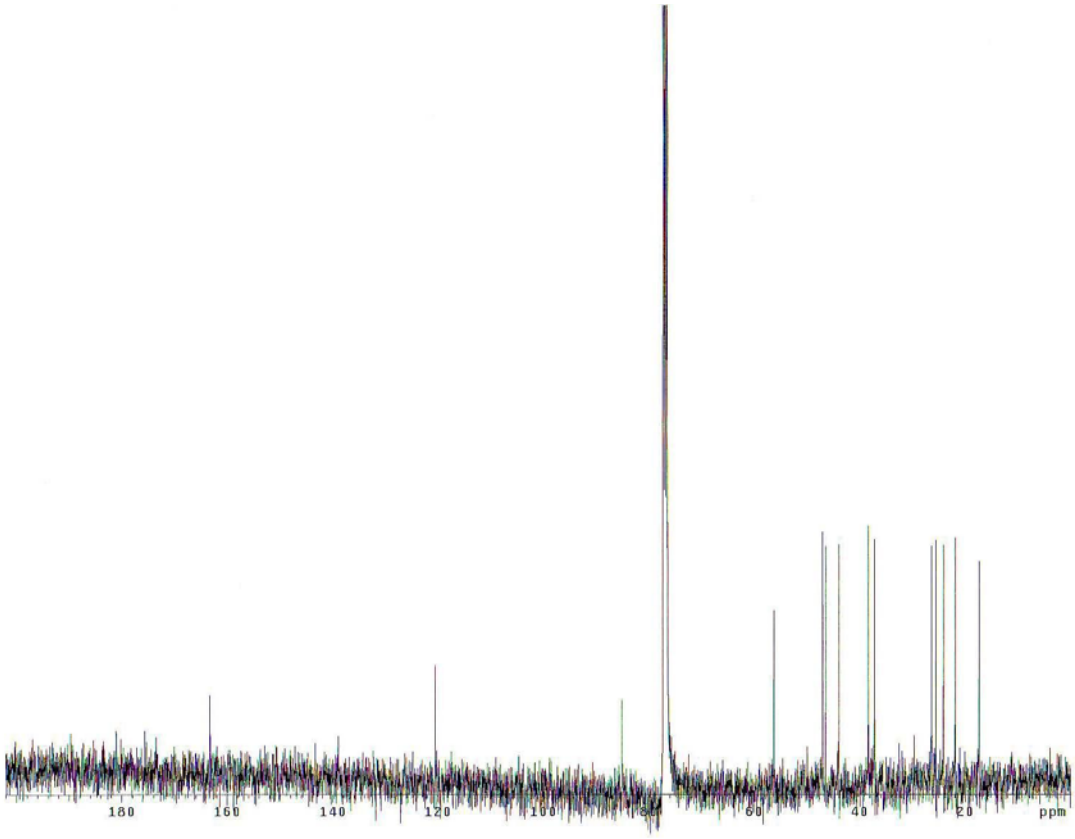
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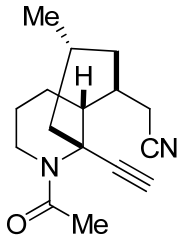
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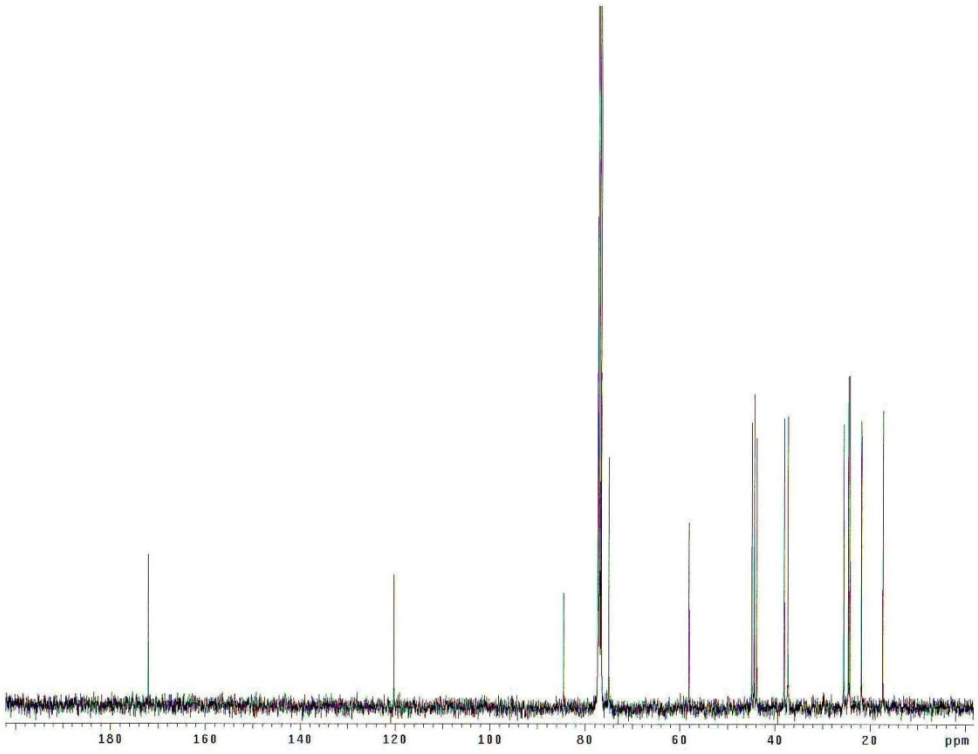
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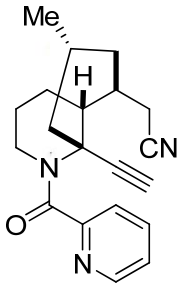
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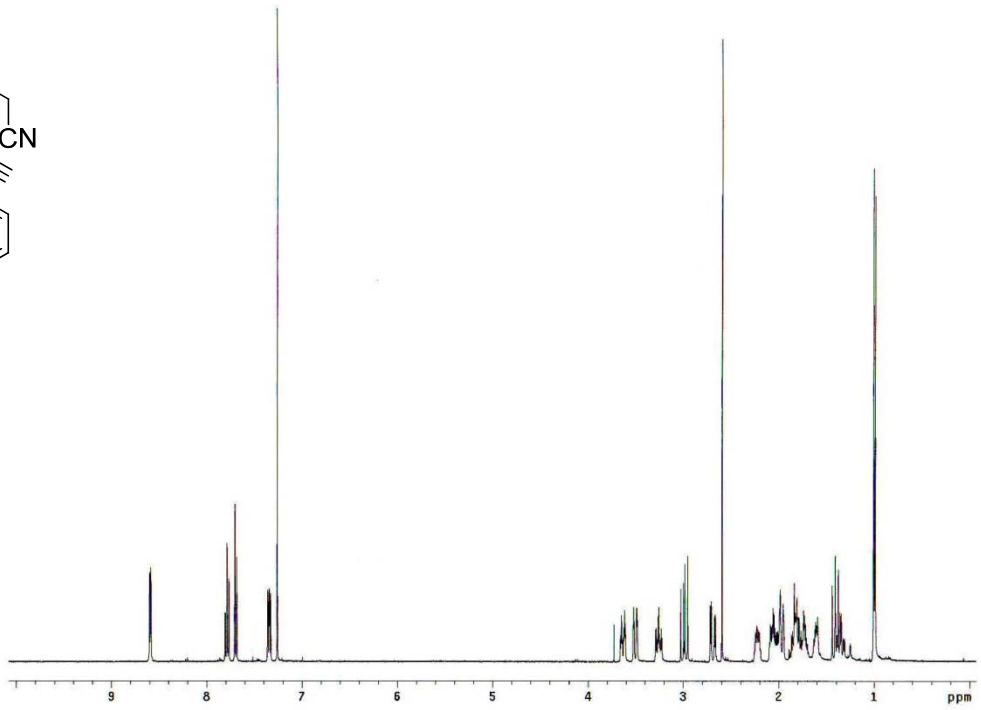
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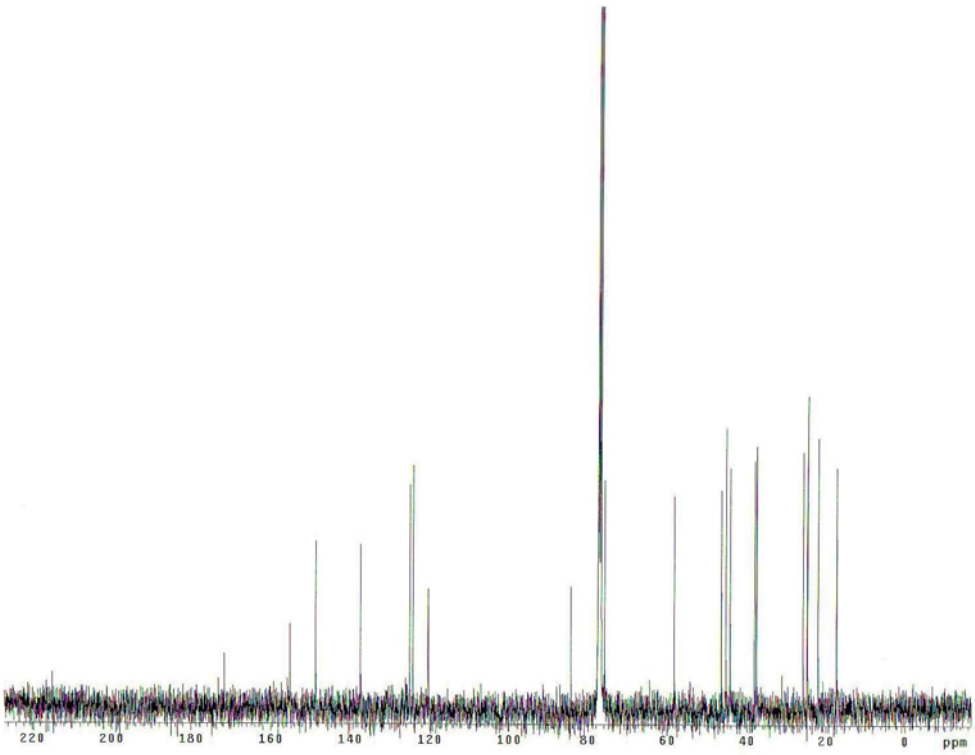
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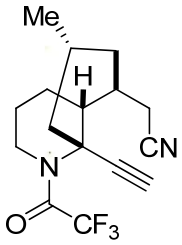
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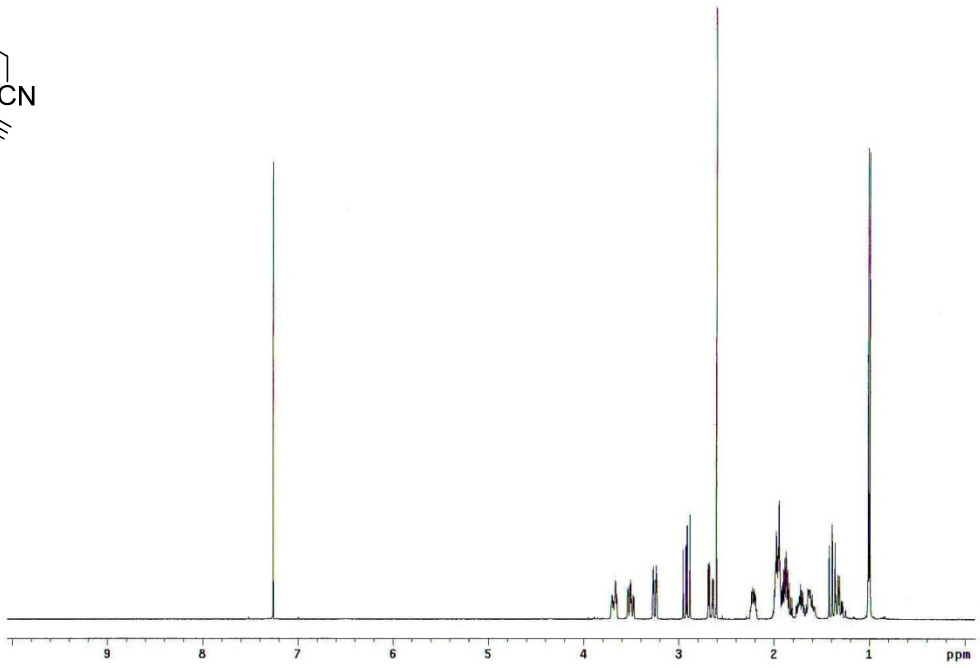
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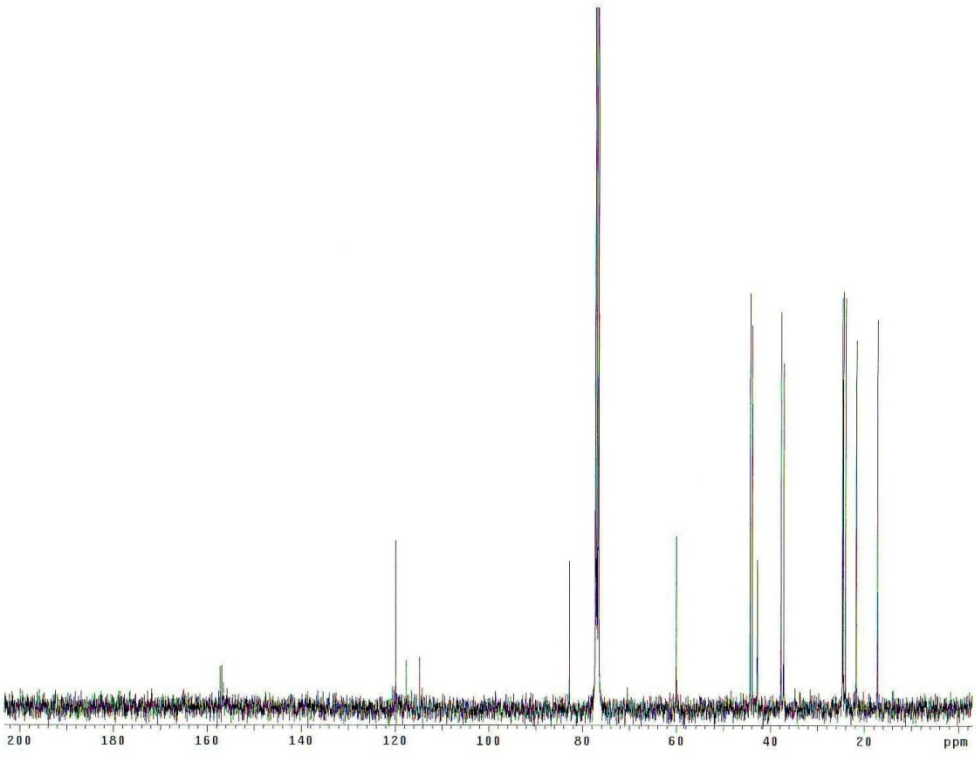
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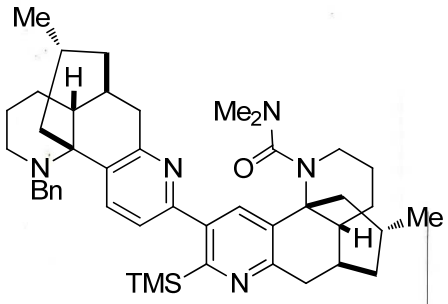
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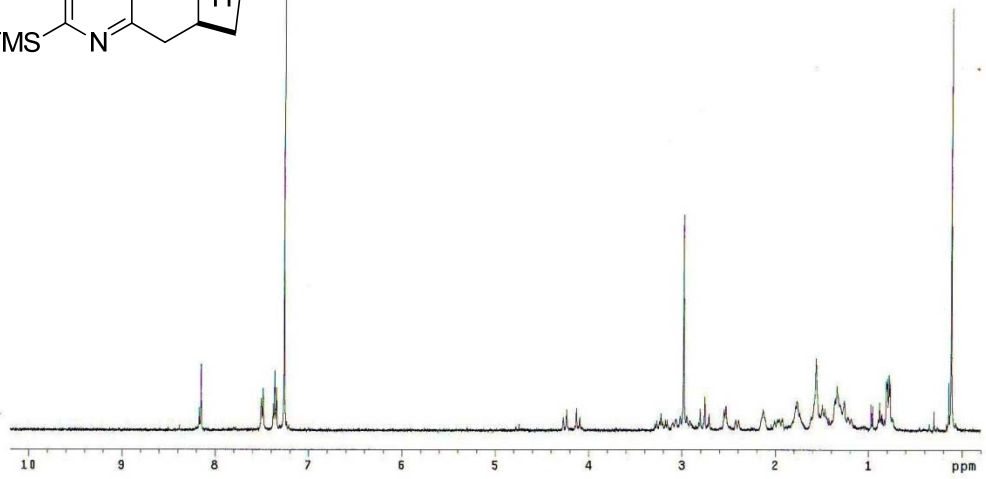
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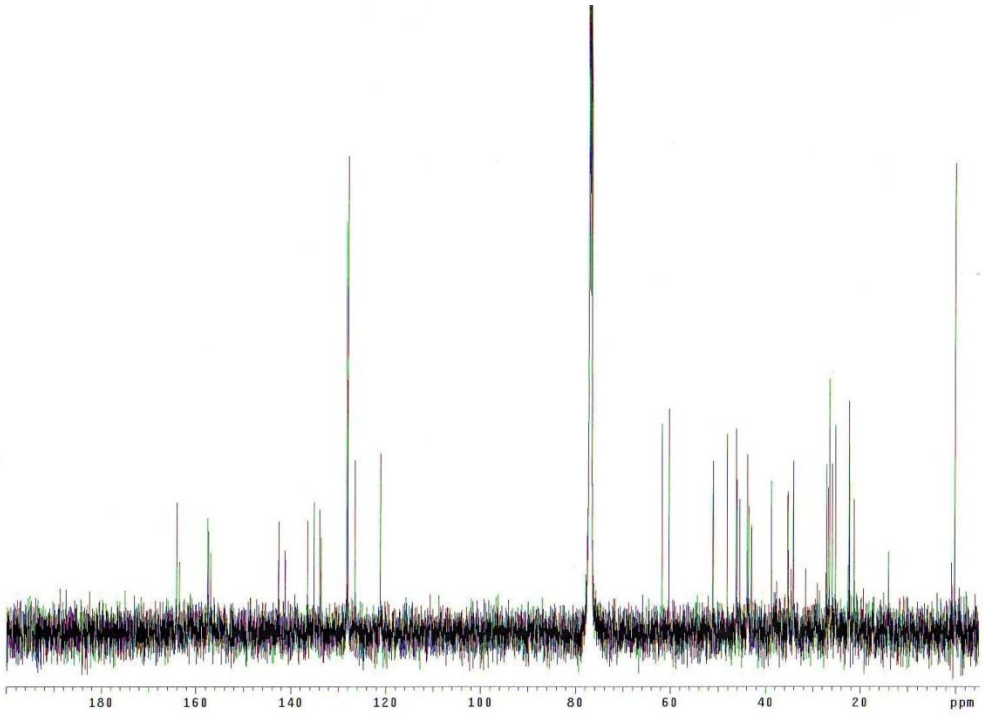
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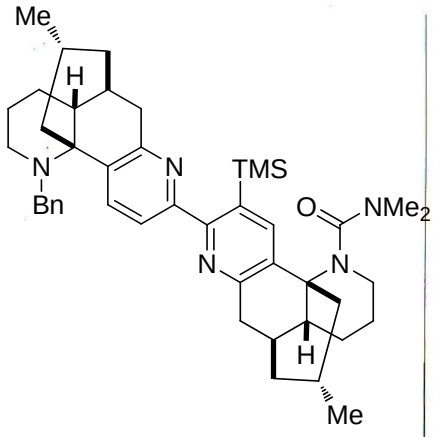
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N
H
Me

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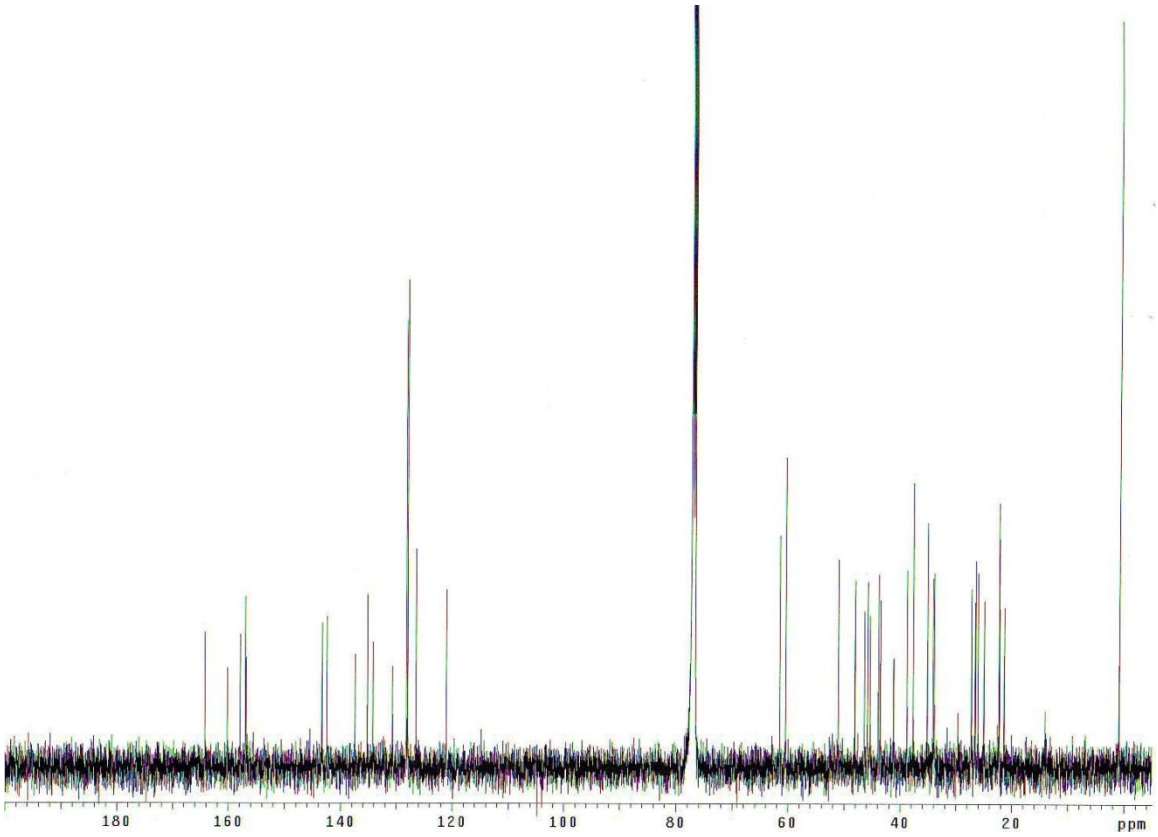
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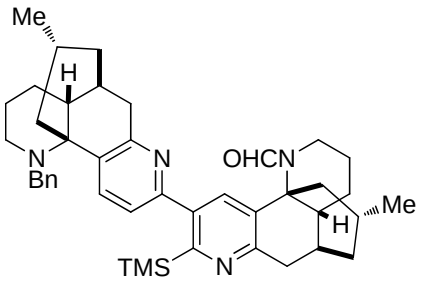
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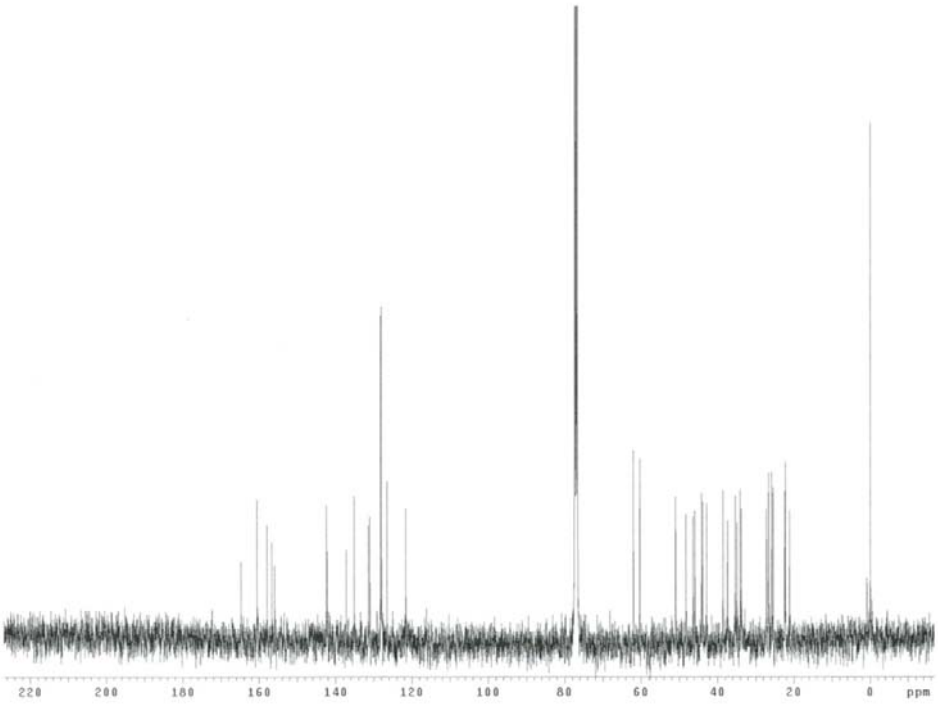
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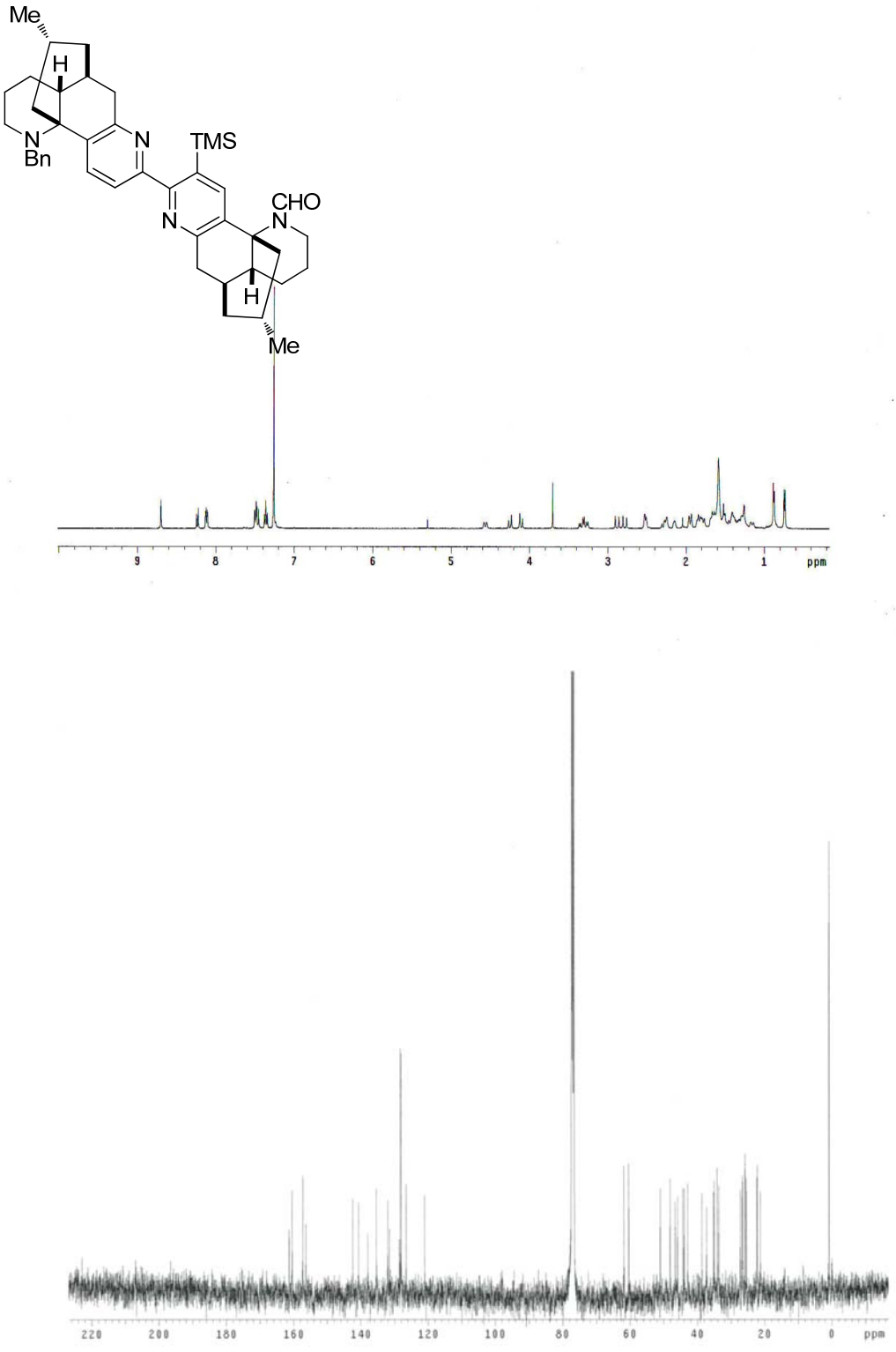
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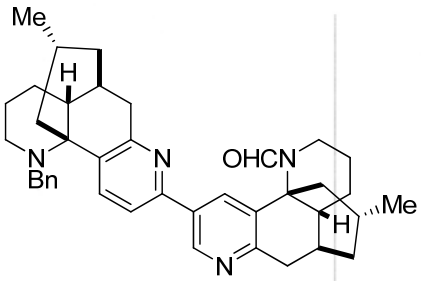
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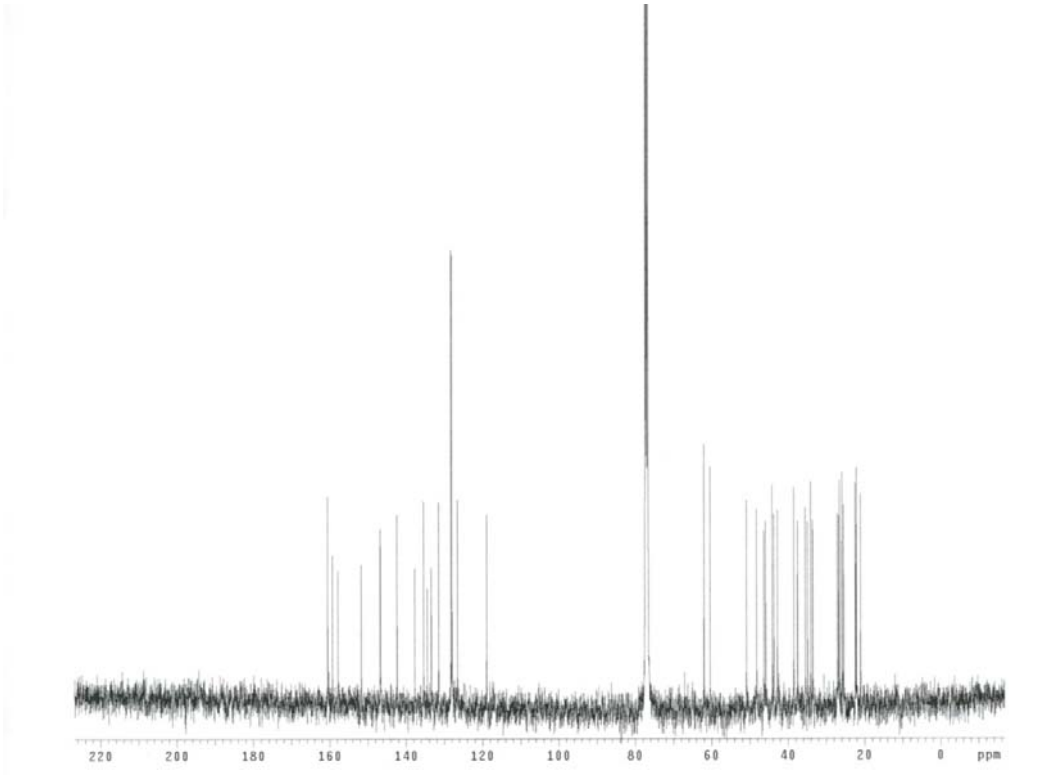
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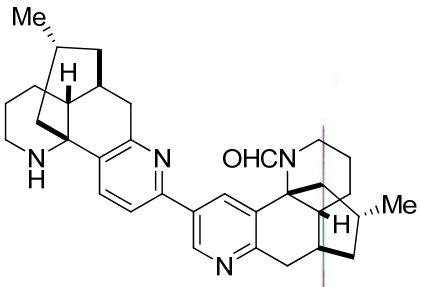
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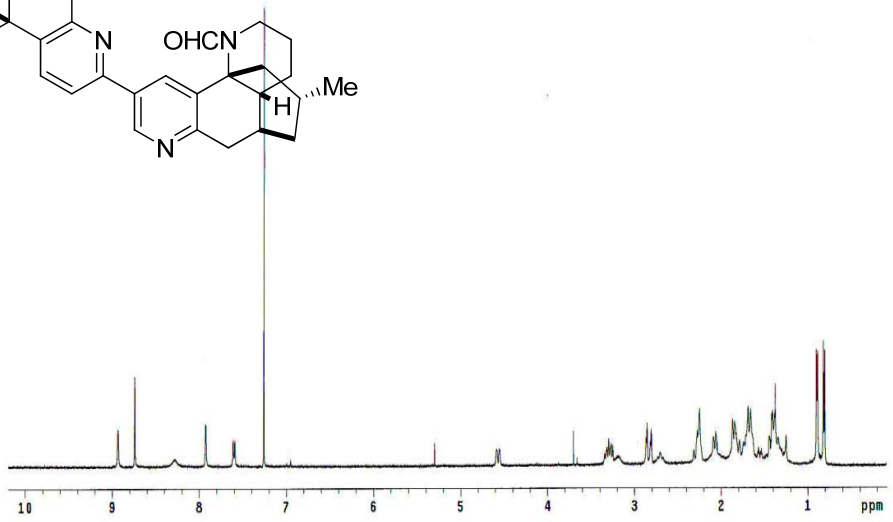
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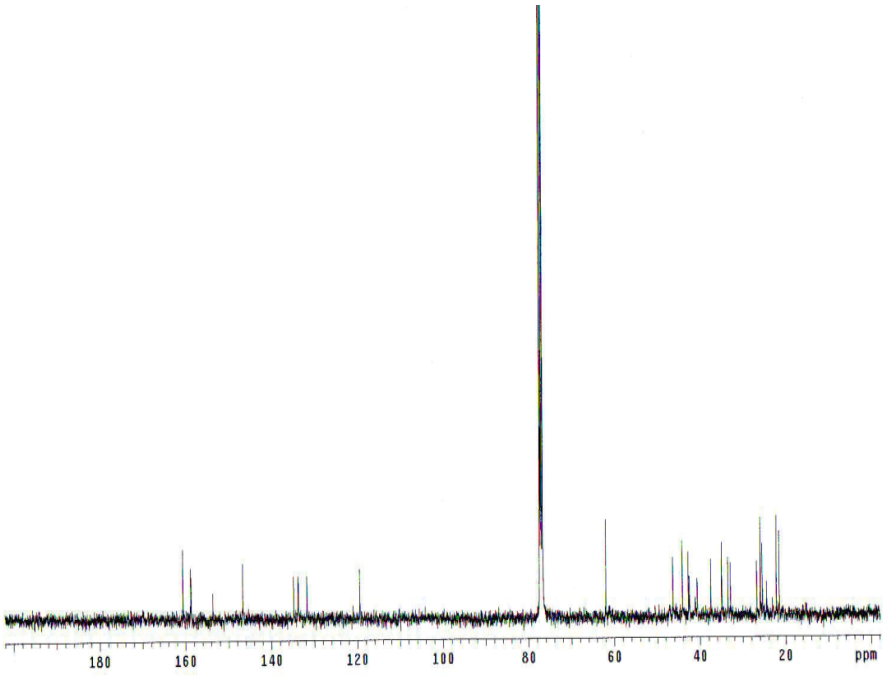
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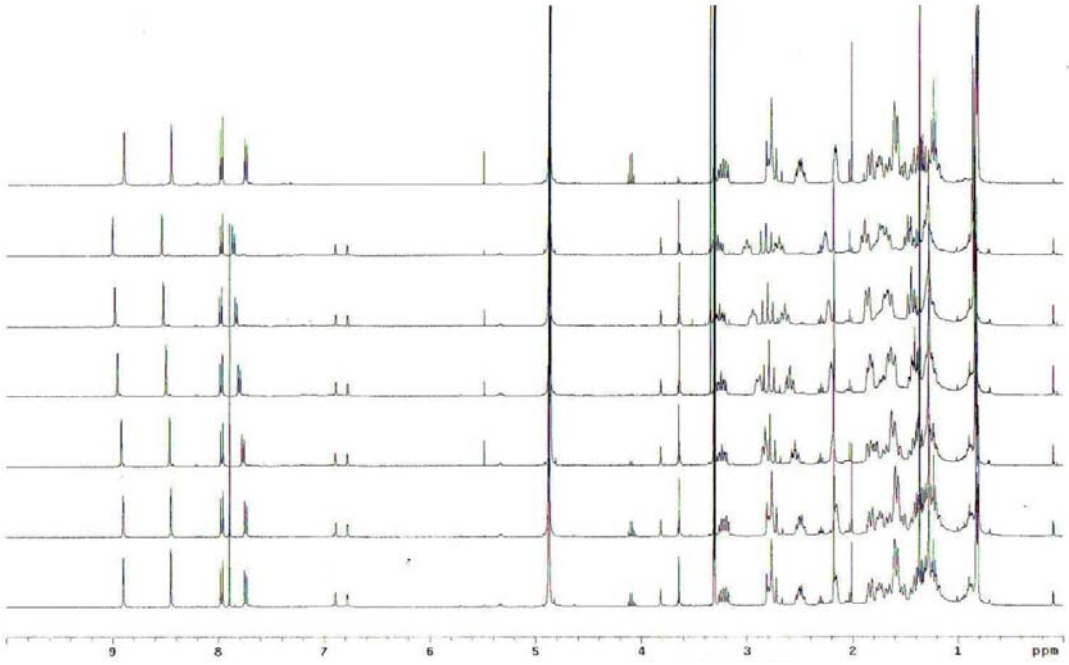

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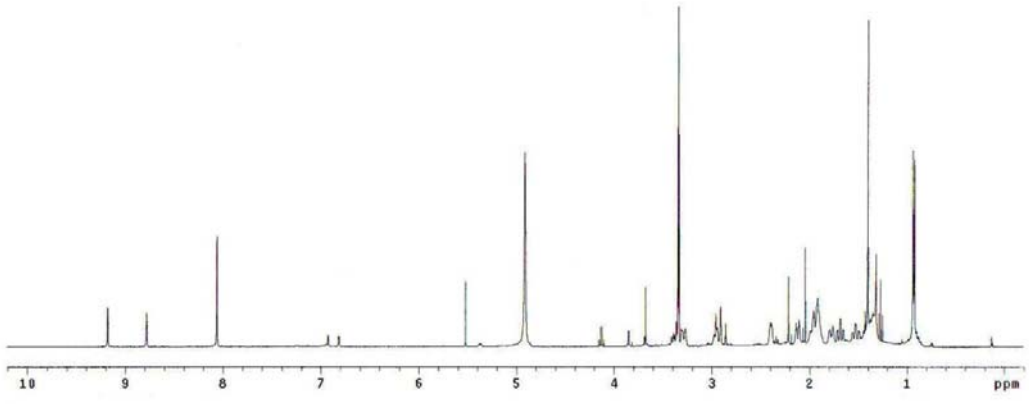

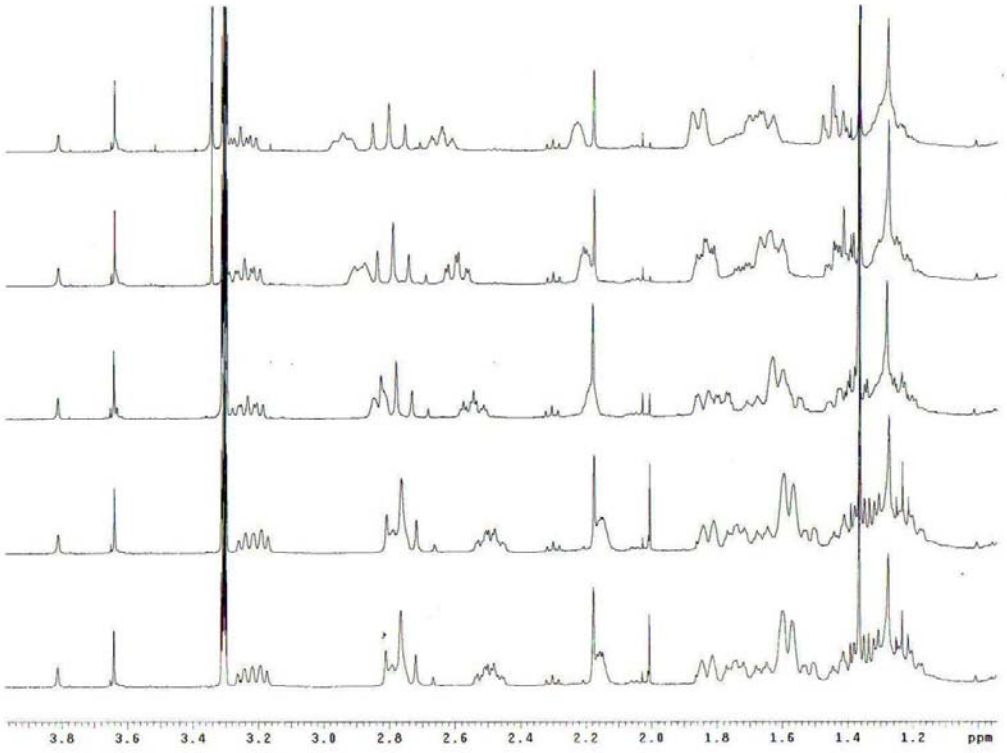

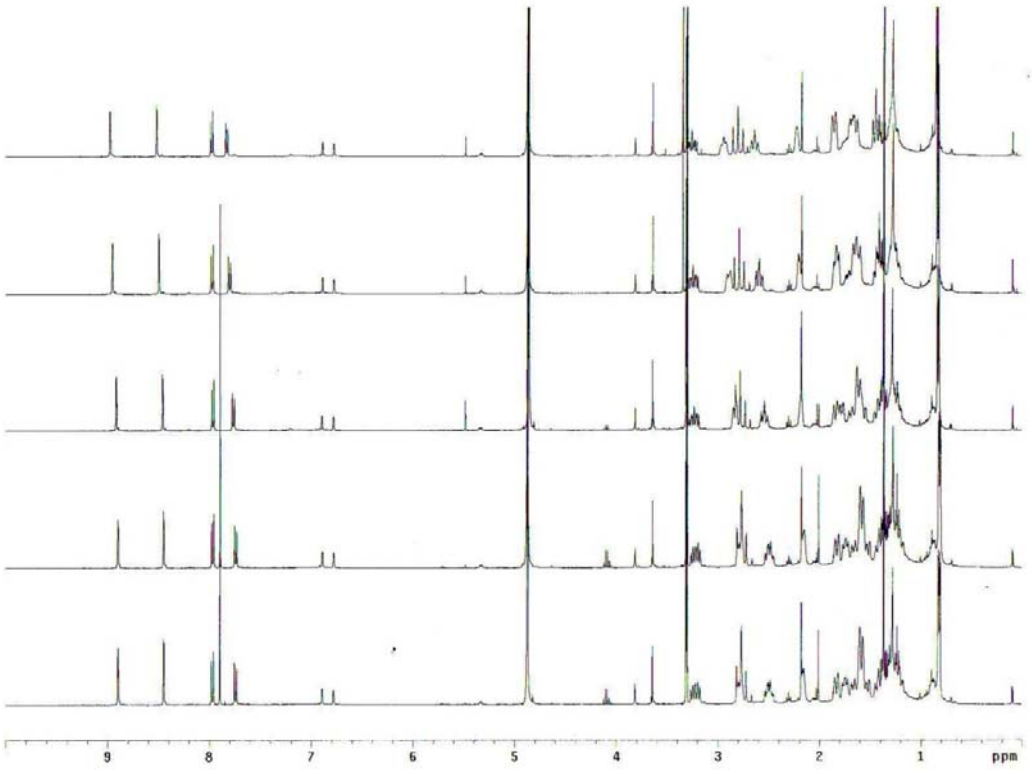

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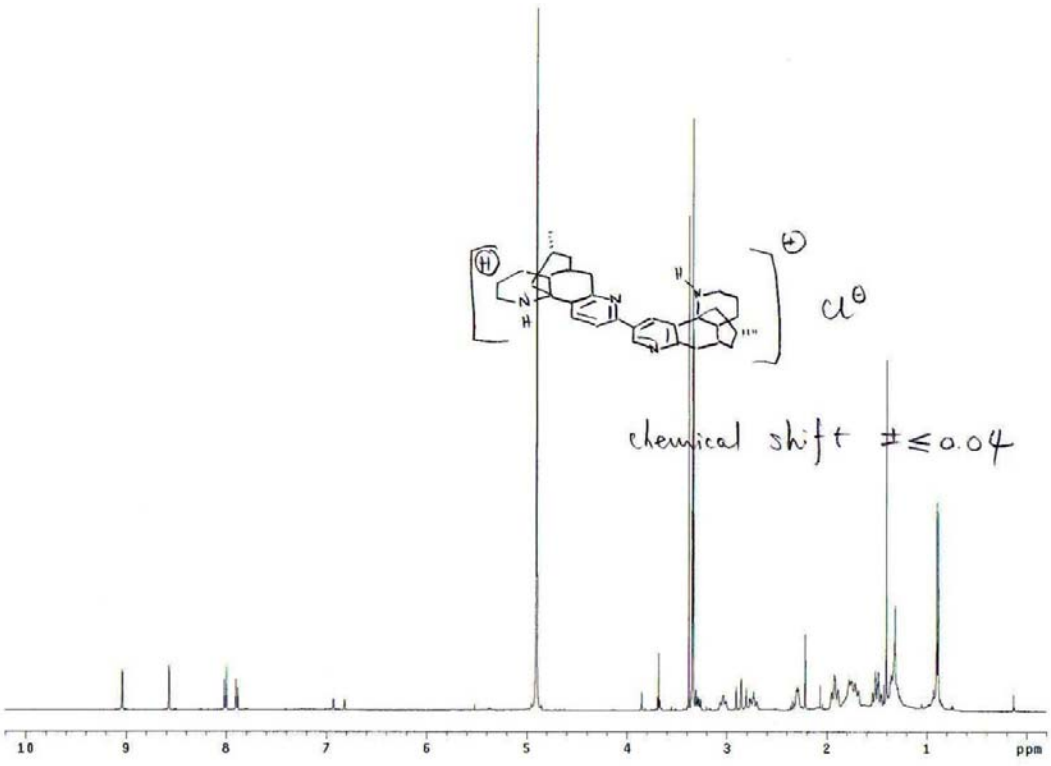
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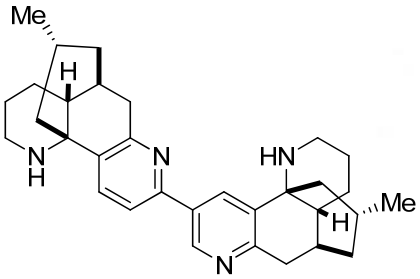
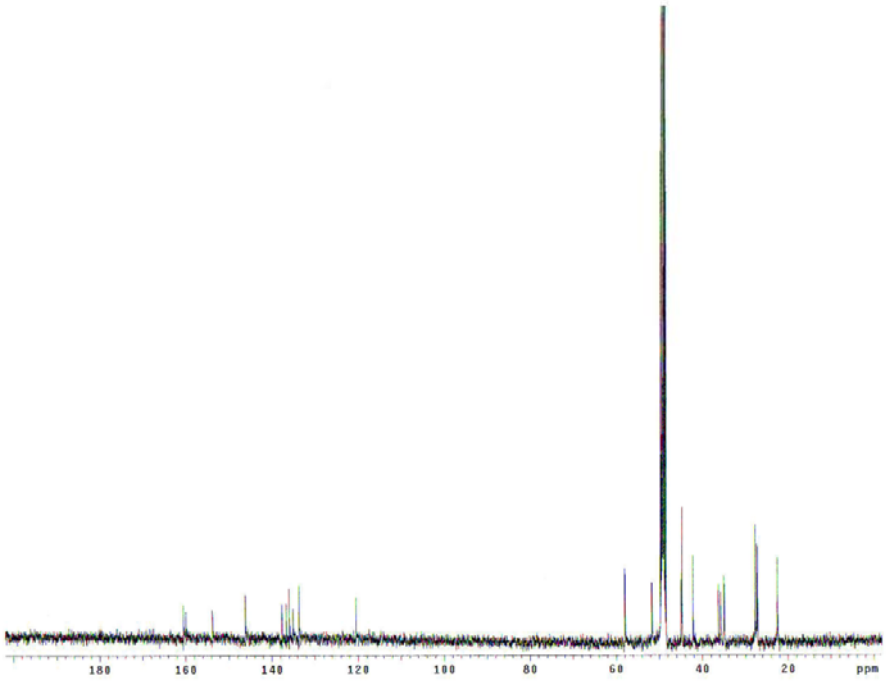


complanadine A (1)



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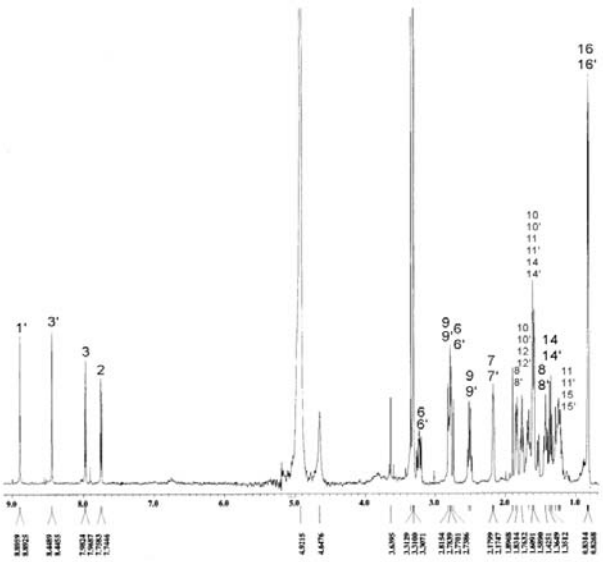
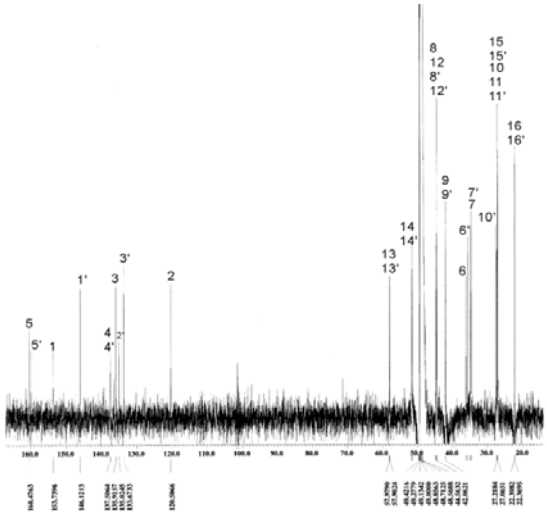
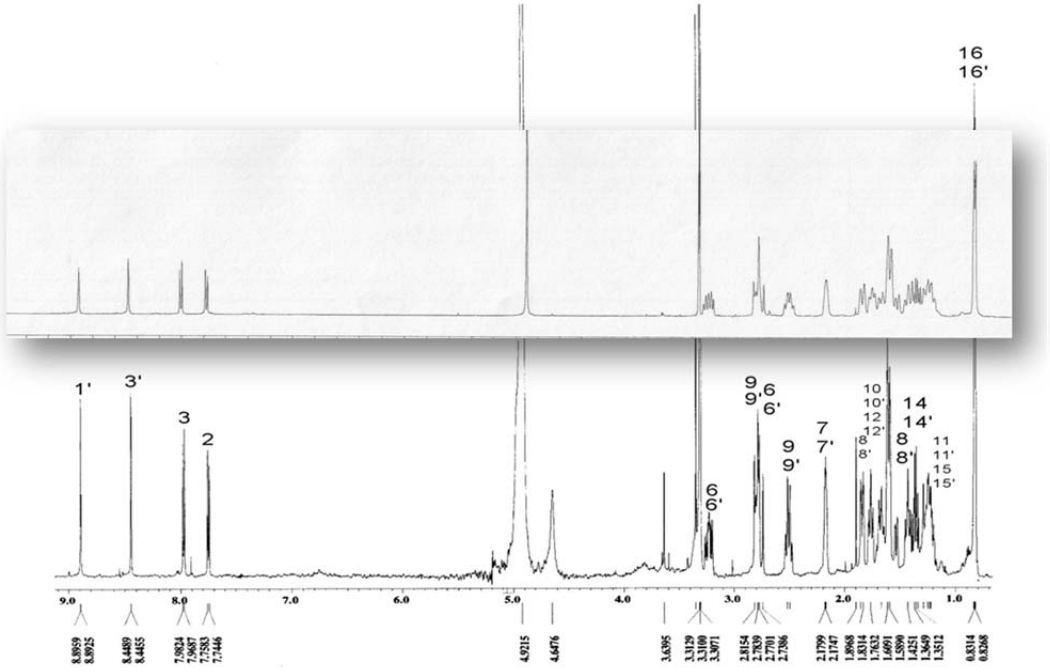


^{1}H NMR spectrum of complanadine A in CD_3OD.

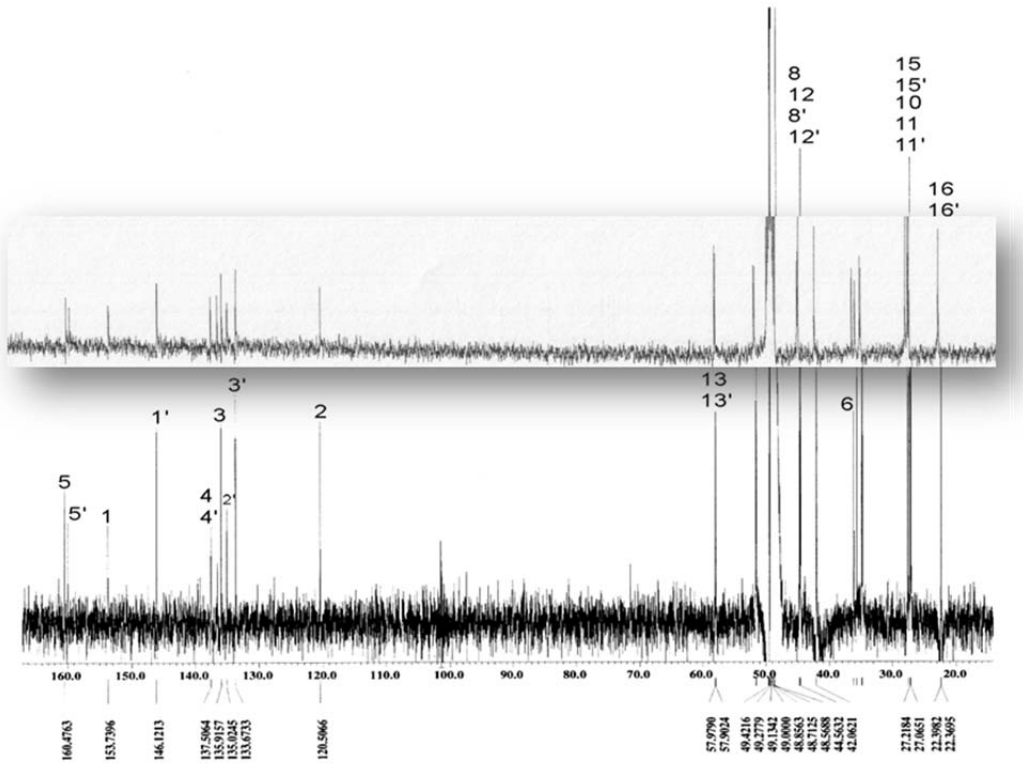


^{13}C NMR spectrum of complanadine A in CD_3OD.

Spectra overlay (synthetic over isolated):



^{1}H NMR spectrum of complanadine A in CD_3OD.



^{13}C NMR spectrum of complanadine A in CD_3OD.

CHAPTER 3 Dihydroxylation of Alkenes Using Phthaloyl Peroxide

3.1 Introduction

The large-scale preparation of diols from alkenes is one of the major transformations used in industrial chemistry. The production levels of the two major glycols, ethylene glycol (14 million tons/ year) and propylene glycol (1.4 million tons/year), highlight their importance.[1,2] Currently, the industrial production of diols occurs through a two-stage process;[3] oxidation of the parent alkene to the corresponding epoxide followed by a subsequent hydration step. Although the epoxidation step has been optimized, a significant amount of waste (>10%) is routinely generated during the epoxide hydrolysis reaction. Besides ethylene and propylene glycol a variety of other vicinal diols are used as solvents and starting materials for polymers, fine chemicals, pharmaceuticals, cosmetics, and cleaners. To date, the direct dihydroxylation of alkenes for the large-scale production of diols has not been feasible.

Phthaloyl peroxide **3.2** had previously been examined as a reagent for the dihydroxylation of alkenes (Figure 3.1). The reaction of phthaloyl peroxide **3.2** with alkenes, primarily stilbenes and styrenes, was studied by Greene and coworkers generating the corresponding five and eight membered lactones.[3,4] These can be readily hydrolyzed to generate diol products. Recently a related derivative, cyclopropylmalonyl peroxide, was found to have similar reactivity, generating diol products from stilbenes and styrenes.[5] We sought to investigate the ability of the intermediate lactones to undergo reaction a reaction with hydrogen peroxide in the presence of base to regenerate the starting phthaloyl peroxide and thus allow a catalytic cycle.

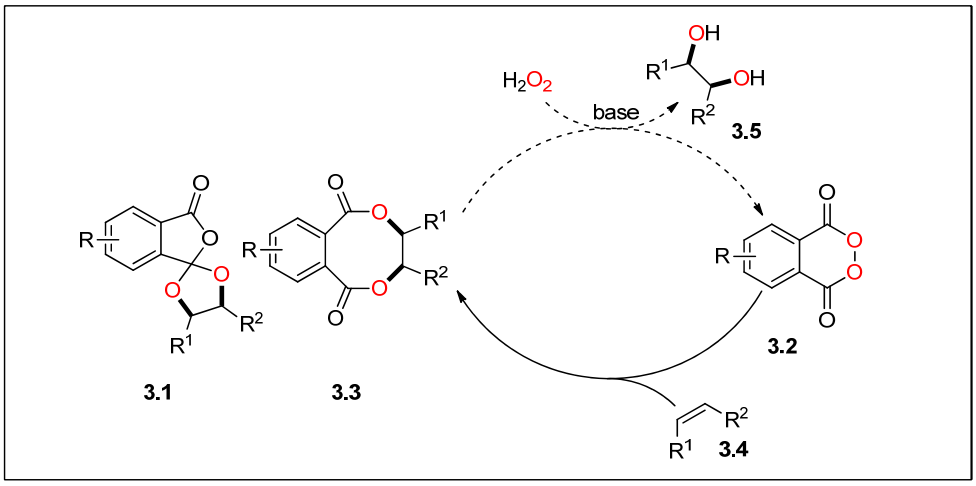
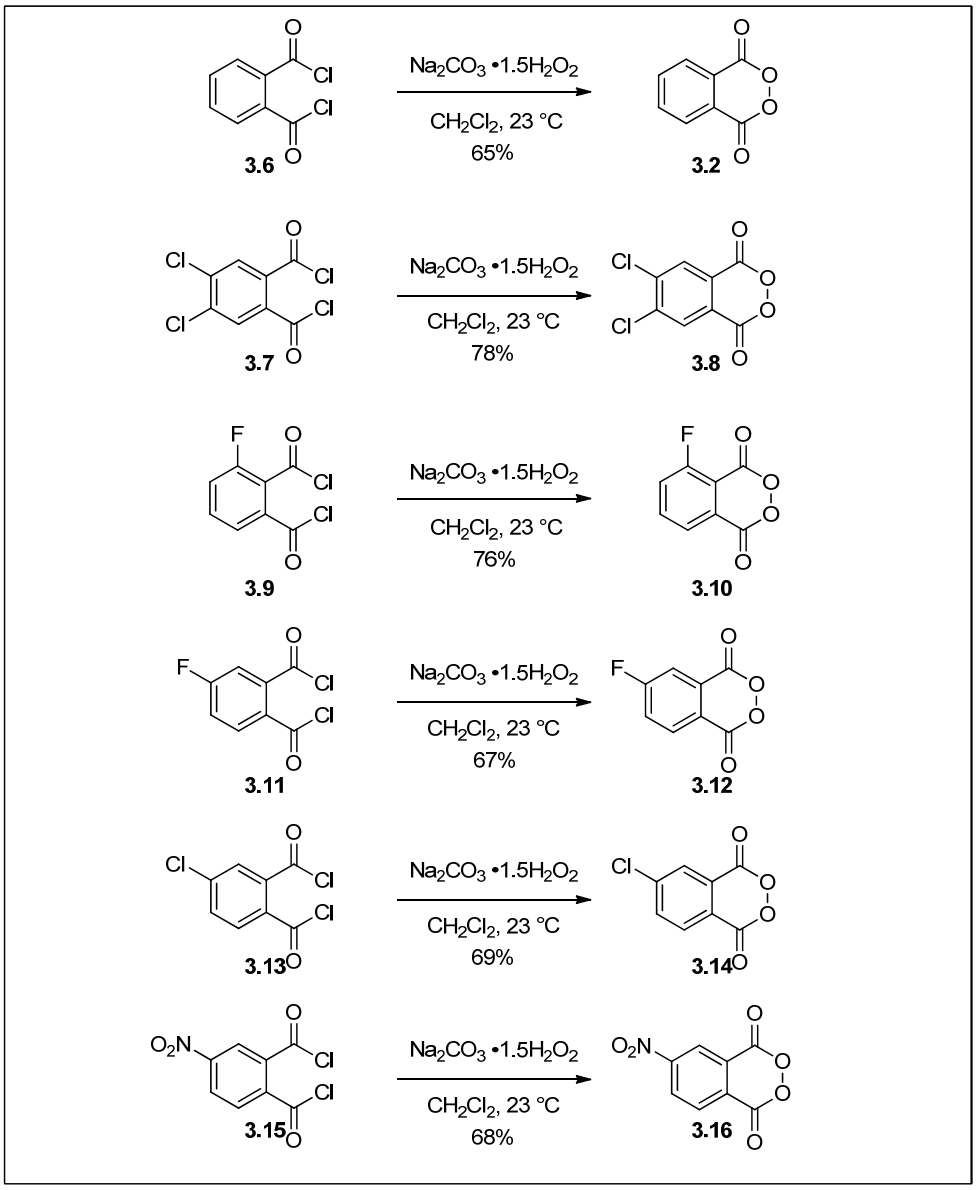


Figure 3.1. Proposed catalytic phthaloyl peroxide **3.2** mediated dihydroxylation.

3.2 Optimized Phthaloyl Peroxide Synthesis

Use of the existing methods for the synthesis of phthaloyl peroxide **3.2** were unreliable and frequently generated explosive by-products.[6] After screening numerous hydrogen peroxide sources we found the used of sodium percarbonate $Na_2CO_3 \bullet H_2O_2$ in dichloromethane proved optimal.[7] (Scheme 3.1). These conditions allowed the synthesis phthaloyl peroxide **3.2** and related derivatives on the gram scale. Recrystallization was possible yielding high purity phthaloyl peroxide **3.2** using pentane-benzene mixtures. A series of phthaloyl peroxide derivatives were prepared and found to have variable stabilities declining from **3.6** to **3.16**.

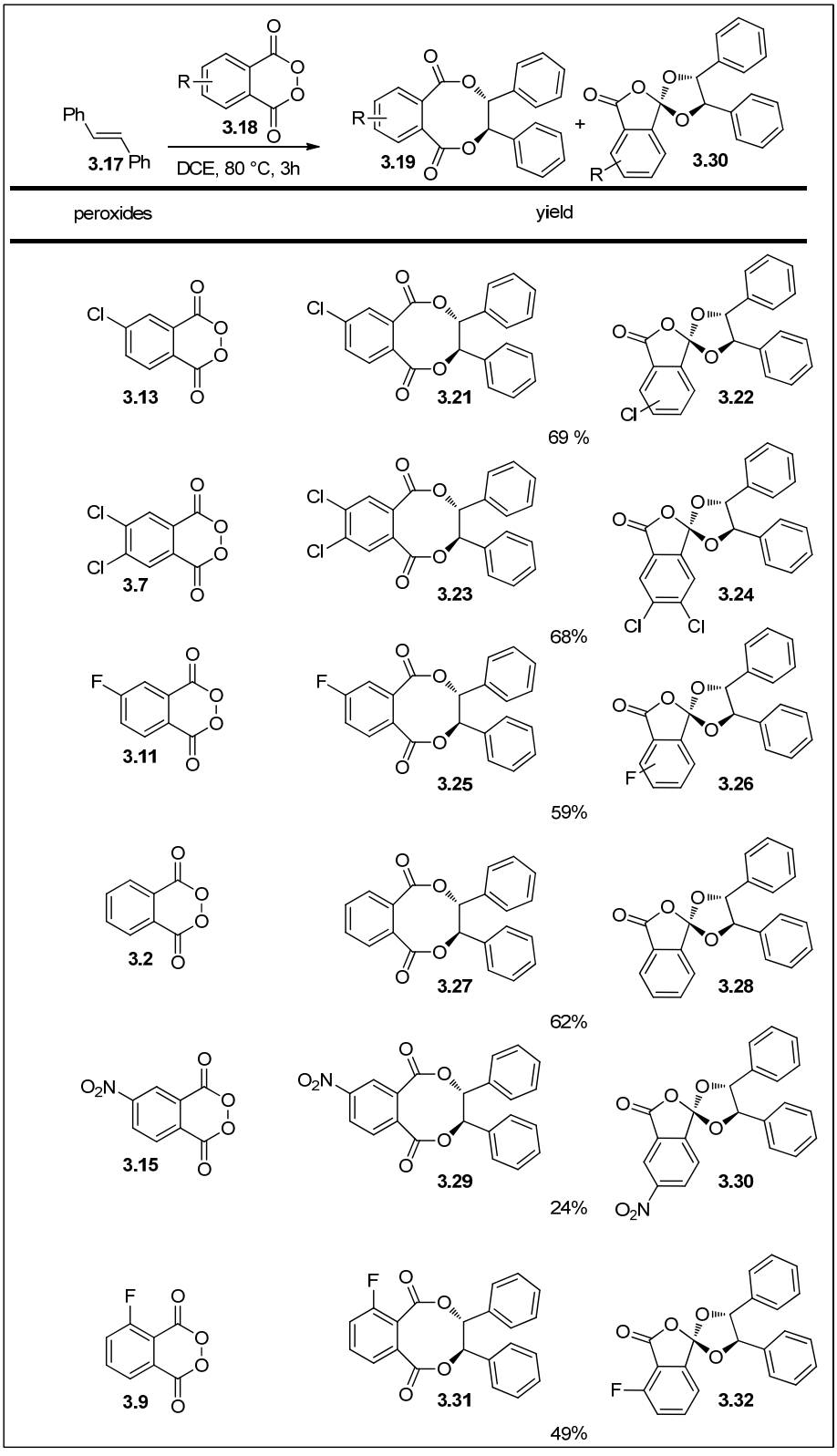
Scheme 3.1: The synthesis of phthaloyl peroxide **3.2** and related derivatives.



3.3 Scope and Generality of Phthaloyl Peroxide Derivatives in the Dihydroxylation of alkenes

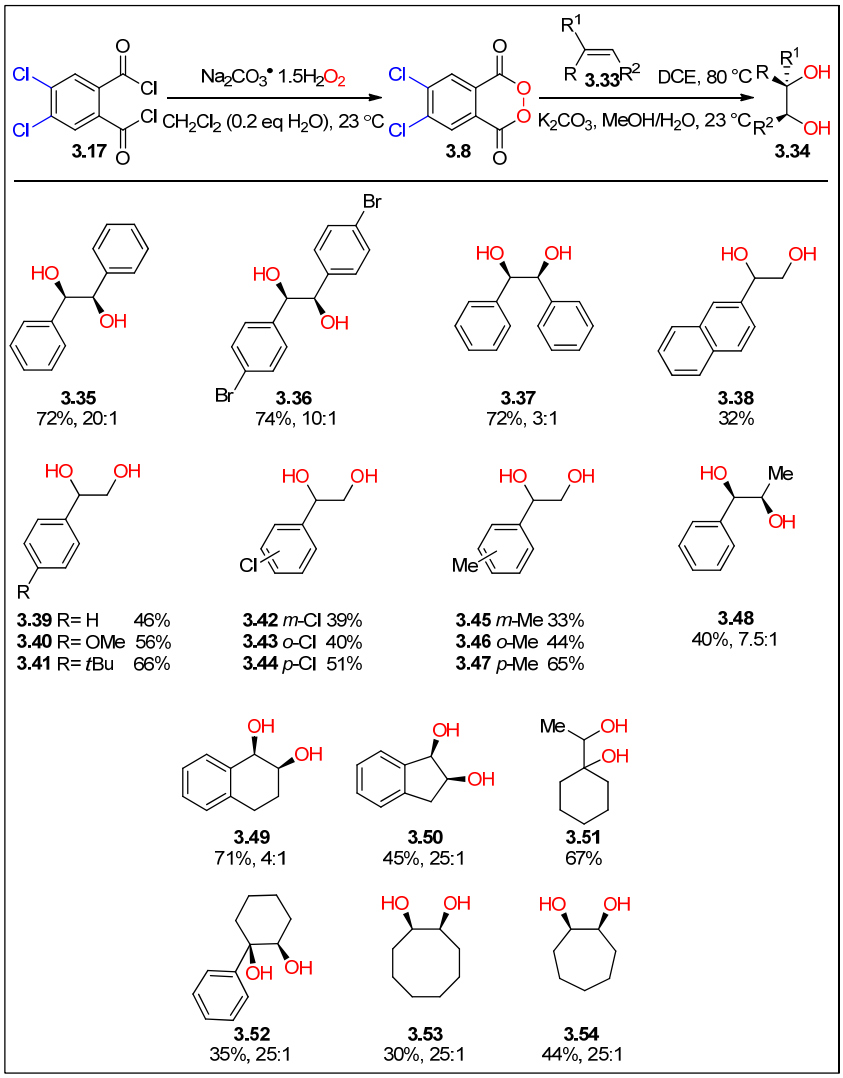
With access to phthaloyl peroxide **3.7** we examined its reactivity with stilbene **3.17** (Table 3.1). From the study 3,4-dichloro phthaloyl peroxide **3.7** was selected for additional investigations as it possesses a good combination of reactivity, availability, and, interestingly, stability. We found, in general, the unsymmetric peroxides had lower stability, possibly as result of polarizing the molecule.

Table 3.1. Reaction of phthaloyl peroxide derivatives with stilbene 3.17.



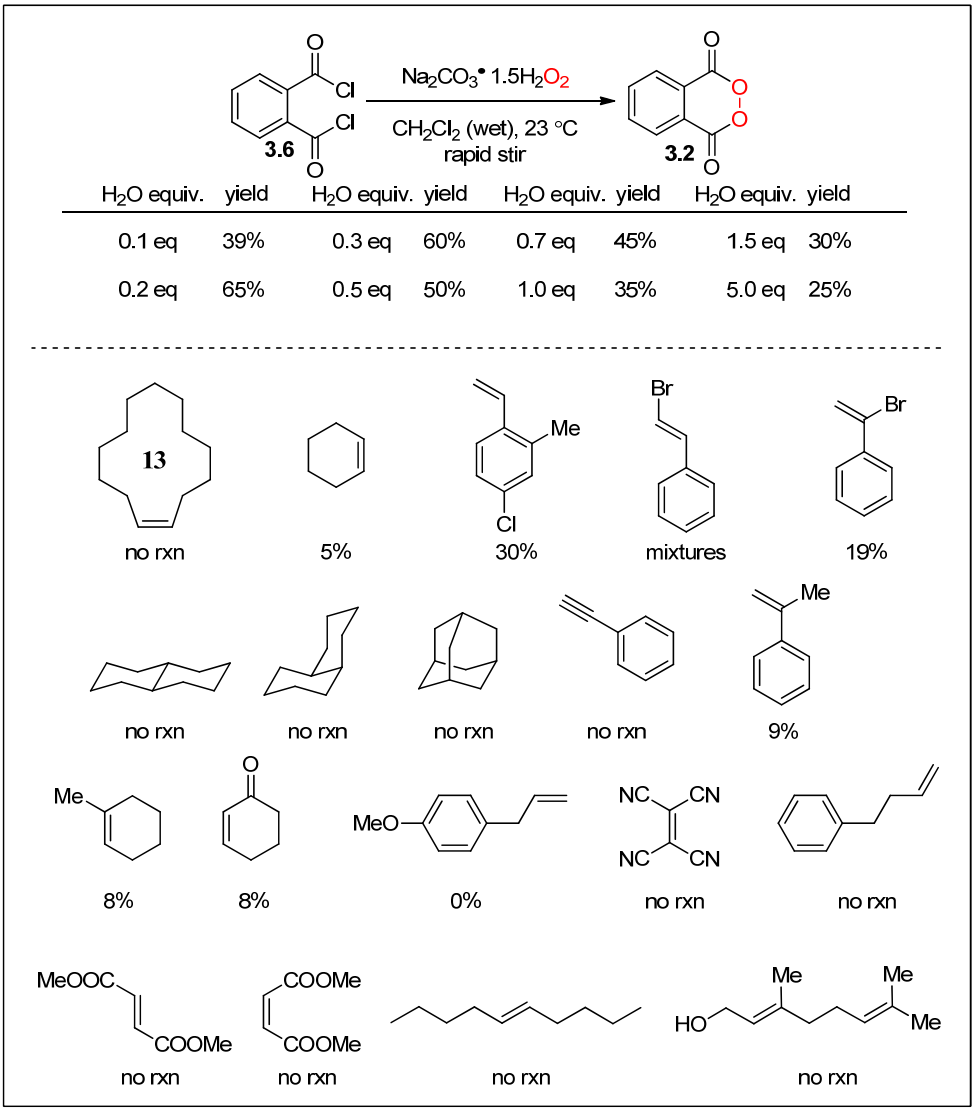
The scope and generality of the reaction, to date, is shown in Table 3.2. The phthaloyl peroxide **3.7** can react with stilbene, indene and styrene derivatives in efficient yield and good stereoselectivities. The reaction was also extended to cycloalkenes to give diol product such as **3.52**, **3.53**, **3.54** in variable yield. This was the first instance of isolated olefins (without conjugation to an arene) undergoing reaction with a phthaloyl peroxide.

Table 3.2. Dichlorophthaloyl peroxide **3.7** mediated dihydroxylation of alkenes.



As the synthesis of phthaloyl peroxide **3.2** seemed to be inconsistent we examined the effects that water has on the reaction. We found the used of dichloromethane that was "wet" provided the most consistent results. This "wet" solvent can be easily prepared by combining dichloromethane and water, shaking, and separating the dichloromethane layer. Use of this pretreated solvent provided the most consistent results.

Scheme 3.2. Role of water in phthaloyl peroxide **3.2** synthesis and failed efforts for dihydroxylation.



3.4 Conclusion

The development of a new, general synthesis of phthaloyl peroxide and related derivatives allowed the testing of several new reagents for their ability to oxidatively functionalize alkenes. For the first time the reaction of phthaloyl peroxide and isolated olefins was possible. With a better understanding of the reactivity of phthaloyl peroxide additional studies focused on the hydroxylation of arenes was made possible.

3.5 References

1. Schroeder, M., Osmium tetraoxide cis hydroxylation of unsaturated substrates. *Chemical Reviews* **1980,** *80* (2), 187-213.

2. Weissermel, K.; Arpe, H., Industrial Organic Chemistry. *Synthesis-Journal of Synthetic Organic Chemistry* **2004,** (7), 1127-1127.

3. (a) Greene, F. D., Cyclic Diacyl Peroxides. I. Monomeric Phthaloyl Peroxide1. *Journal of the American Chemical Society* **1956,** *78* (10), 2246-2250; (b) Greene, F. D., Cyclic Diacyl Peroxides. II. Reaction of Phthaloyl Peroxide with cis- and trans-Stilbene. *Journal of the American Chemical Society* **1956,** *78* (10), 2250-2254; (c) Greene, F. D.; Rees, W. W., Cyclic Diacyl Peroxides. III.1 The Reaction of Phthaloyl Peroxide with Olefins. *Journal of the American Chemical Society* **1958,** *80* (13), 3432-3437; (d) Greene, F. D., Cyclic Diacyl Peroxides. IV.1,2 Phthaloyl Peroxide-carbonyl-O18. *Journal of the American Chemical Society* **1959,** *81* (6), 1503-1506; (e) Greene, F. D.; Rees, W. W., Cyclic Diacyl Peroxides. VI.1 Reaction of Phthaloyl Peroxide with Diarylacetylene. *Journal of the American Chemical Society* **1960,** *82* (4), 893-896; (f) Greene, F. D.; Rees, W. W., Cyclic Diacyl Peroxides. V.1 Reaction of Phthaloyl Peroxide with Norbornylene. *Journal of the American Chemical Society* **1960,** *82* (4), 890-893; (g) Greene, F. D.; Kazan, J., Preparation of Diacyl Peroxides with N,N'-Dicyclohexylcarbodiimide1. *Journal of Organic Chemistry* **1963,** *28* (9), 2168-2171.

4. Fujimori, K.; Oshibe, Y.; Hirose, Y.; Oae, S., Thermal decomposition of diacyl peroxide. Part 11. ^{18}O-Scrambling in carbonyl-^{18}O-labelled phthaloyl peroxide, a cyclic Case III diacyl peroxide. Extremely large return of unescapable acyloxyl radical pair. *Journal of the Chemical Society, Perkin Transactions 2* **1996,** (3), 413-417.

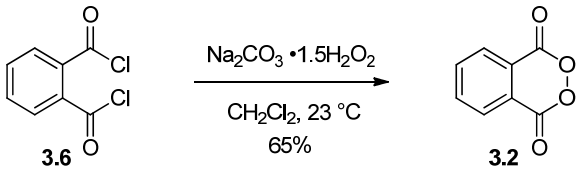
5. (a) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O., Alkene Syn Dihydroxylation with Malonoyl Peroxides. *Journal of the American Chemical Society* **2010,** *132* (41), 14409-14411. (b) Yuan, C.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. Synthesis and reaction of phthaloyl peroxide derivatives, potential organocatalysts for the stereospecific dihydroxylation of alkenes." *Tetrahedron Lett.* **2011**, *52*, 2540-2542.

6. Russell, K. E., The Preparation of Phthalyl Peroxide and its Decomposition in Solution.

7. Bauer, K.; Garbe, D.; Surburg, H. Ullmann's Encyclopedia of Industrial Chemistry. *Ullmann's Encyclopedia of Industrial Chemistry* **1988,** *11*.

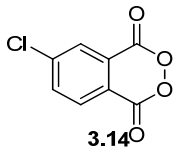
3.6 Experimental Section

Representative procedure for phthaloyl peroxide synthesis:



To a solution of phthaloyl chloride **3.6** (0.40 g, 1.5 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL), solid sodium percarbonate (Aldrich available H_2O_2: 20-30%) (0.34 g, 2.2 mmol, 1.5 equiv) was added in one portion. The heterogeneous reaction mixture was stirred vigorously for 3 hours (rapid stirring is required). The reaction mixture was filtered through celite and concentrated to provide the phthaloyl peroxide **3.2** as white solid (0.27 g, 78%) matching existing characterization data.[1]

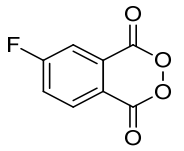
m-Chlorophthaloyl Peroxide **3.14**



Following the representative procedure peroxide **3.14** was prepared as a white solid (69%). This compound will slowly decompose. If necessary, recrystallization from benzene/hexanes can be performed.

m.p. 63.5-64.5 °C decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (m, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.97 (dd, J = 1.5 and 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.2, 161.0, 143.9, 136.8, 131.7, 130.0, 125.0, 121.8;**IR** ν 3447, 1749, 1635 cm^{-1}; **HRMS** calcd. for $C_8H_3O_4Cl^+$ $[M]^+$: 197.9720. Found:197.9719.

o-Fluorophthaloyl Peroxide **3.12**

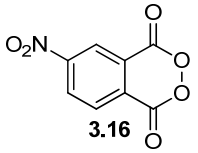


3.12

Following the representative procedure the peroxide **3.12** was synthesized as a white solid (67%). This compound will slowly decompose. If necessary, recrystallization from benzene/hexanes can be performed.

m.p. 57.5-58.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.40 (dd, J = 2.4 and 8.8 Hz, 1H), 7.94 (dd, J = 2.4 and 7.8 Hz, 1H), 7.70 (dt, J = 2.4 and 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161,1, 161.0, 133.7, 133.6, 124.5, 124.3, 117.1, 116.9; **IR** v 3083, 1761, 1607 cm^{-1}; **HRMS** calcd. for $C_8H_3O_4F^+$ $[M]^+$: 182.0015. Found:182.0014.

m-Nitrophthaloyl Peroxide **3.16**

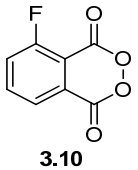


3.16

Following the representative procedure peroxide **3.16** was prepared as pale yellow oil (68%). This compound quickly decompose at 23 °C and must be used directly.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (d, J = 2.4 Hz, 1H), 8.80 (dd, J = 2.4 and 8.4 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H); **IR** v 3111, 1784, 1757, 1541 cm^{-1}.

o-Fluorophthaloyl Peroxide **3.10**

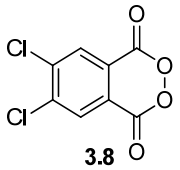


3.10

Following the representative procedure peroxide **3.10** was prepared as a white solid (76%). This compound will slowly decompose. If necessary, recrystallization from benzene/hexanes can be performed.

m.p. 133.2-134.5 °C, decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.4 Hz, 1H), 8.03 (dt, J = 4.8 and 8.4 Hz, 1H), 7.14 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.3, 160.6, 138.7, 138.6, 126.6, 125.2, 124.9, 124.7; **IR** ν 1786, 1748, 1291, 906 cm^{-1}; **HRMS** calcd. for $C_8H_3O_4F^+$ $[M]^+$: 182.0015. Found:182.0014.

3,4-Dichlorophthaloyl Peroxide **3.8**

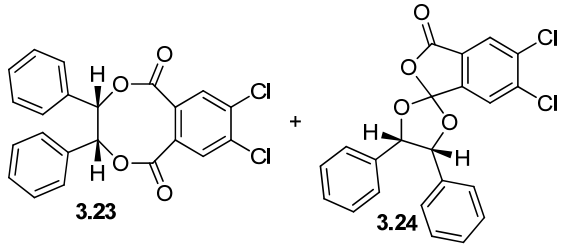


3.8

Following the general procedure, the peroxide **3.8** (0.5 g, 1.83 mmol) was synthesized as a white solid (333 mg, 78%). This compound displayed improved stability relative to the other peroxides. If necessary, recrystallization from benzene/hexanes can be performed.

m.p. 89-91 °C, decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.38 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.4, 142.4, 131.8, 122.6; **IR** ν 1748, 906 cm^{-1}; **HRMS** calcd. for $C_8H_4O_4Cl_2^+$ $[M]^+$: 231.9330. Found:231.9331 .

Representative dihydroxylation procedure:



3.23 **3.24**

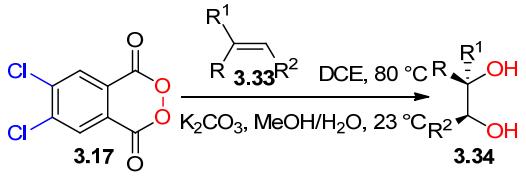
Procedure 1 (synthesis of lactones): Solid *trans*-stilbene (40.0 mg, 0.22 mmol, 1.0 eq) and 3, 4-dichlorophthaloyl peroxide **3.7** (80 mg, 0.34 mmol, 1.5 eq) were dissolved in dichloroethane (4 mL) and placed in an oil bath at 80 °C under nitrogen. After stirring for 8 hours the reaction mixture was cooled to 23 °C, diluted with sat. Na_2CO_3 (aq., 10 mL) and sat. $Na_2S_2O_3$ (aq., 10 mL), and extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (hexanes:EtOAc 20:1 to 5:1) to afford the eight-membered ring product **3.23** (20 mg, 22%) as light yellow oil and five-membered ring product **3.24** as a white solid (42 mg, 46%).

Lactone **3.23:**

R_f Hexanes:EtOAc = 5:1, 0.85. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (s, 2H), 7.31-7.43 (m, 10H), 6.16 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.8, 137.1, 134.1, 133.6, 130.5, 129.3, 128.8, 127.4, 89.8; **IR** *v* 3034, 1740, 1259 cm^{-1}; **HRMS** calcd. for $C_{23}H_{18}O_5Cl_2Na^+$ $[M+Na]^+$: 435.0167. Found:435.0161.

Lactone **3.24:**

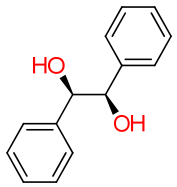
R_f (Hexanes:EtOAc = 5:1) 0.79; **m.p.** 89.5-90.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (s, 2H), 7.31-7.43 (m, 10H), 5.41 (d, J = 11.2 Hz, 1H), 5.24 (d, J = 11.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.3, 163.8, 140.9, 139.9, 137.2, 135.2, 133.9, 129.4, 129.2, 128.9, 128.2, 127.0, 126.9, 126.5, 125.4, 123.3, 88.4, 86.5; **IR** *v* 3384, 1789, 1304 cm^{-1}; **HRMS** calcd. for $C_{23}H_{18}O_5Cl_2Na^+$ $[M+Na]^+$: 435.0167. Found:435.0161.



Procedure 2 (synthesis of diols): Solid *trans*-stilbene (40.0 mg, 0.22 mmol, 1.0 eq) and

3,4-dichlorophthaloyl peroxide (80 mg, 0.34 mmol, 1.5 eq) were dissolved in DCE (4 mL) and placed in an oil bath at 80 °C under nitrogen. After stirring for 8 hours the reaction mixture was cooled to 23 °C and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (3 ml) and H_2O (0.15 mL) and K_2CO_3 (123 mg, 0.89 mmol, 4 eq) were added resulting in a heterogeneous mixture that was vigorously stirred for 10 hours. The reaction was diluted with EtOAc (10 mL). The organic layer was collected and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica (hexanes:EtOAc 10:1 to 1:1) to afford (±)-hydrobenzoin **3.34** (34.2 mg, 72%, *syn*:*anti* = 19:1).

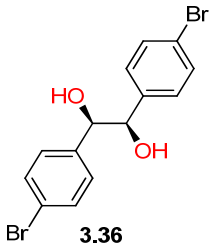
(±)-Hydrobenzoin **3.35**



3.35

Dihydroxylation was performed according to procedure 2 (yield 72%). The diastereoselectivity ratio was *syn*:*anti* = 20:1. Analytical data matched literature.[2]

(±)-1,2-Di-4-bromophenylethane-1,2-diol **3.36**

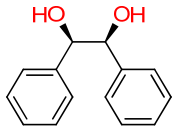


3.36

Dihydroxylation was performed according to procedure 2 (yield 74%). The

diastereoselectivity ratio was *syn*:*anti* = 20:1. Analytical data matched literature.[2]

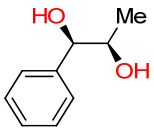
meso-Hydrobenzoin **3.37**



3.37

Dihydroxylation was performed according to procedure 2 (yield 72%). The diastereoselectivity ratio was *syn*:*anti* = 3:1. Analytical data matched literature.[2]

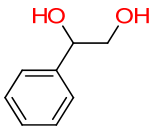
1-Phenylpropane-1,2-diol **3.48**



3.48

Dihydroxylation was performed according to procedure 2 (yield 40%). The diastereoselectivity ratio was *syn*:*anti* = 7.5:1. Analytical data matched literature.[2]

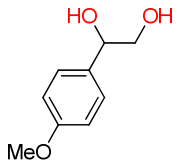
1-Phenylethane-1,2-diol **3.39**



3.39

Dihydroxylation was performed according to procedure 2 (yield 46%). Analytical data matched literature.[2]

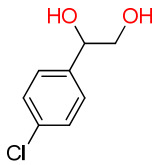
1-(4-Methoxyphthyl)ethane-1,2-diol **3.40**



3.40

Dihydroxylation was performed according to procedure 2 (yield 56%). Analytical data matched literature.[2]

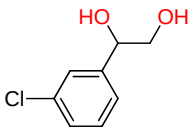
1-(4-Chlorophenyl)ethane-1,2-diol **3.44**



3.44

Dihydroxylation was carried out according to general procedure 2 (yield 51%). All the experimental data matched with literature.[2]

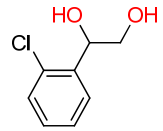
1-(3-Chlorophenyl)ethane-1,2-diol **3.39**



3.39

Dihydroxylation was performed according to procedure 2 (yield 40%). Analytical data matched literature.[3]

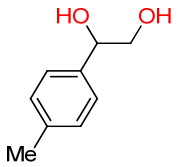
1-(2-Chlorophenyl)ethane-1,2-diol **3.42**



3.42

Dihydroxylation was performed according to procedure 2 (yield 39 %). Analytical data matched literature.[2]

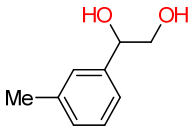
1-(4-Methylphenyl)ethane-1,2-diol **3.47**



3.47

Dihydroxylation was performed according to procedure 2 (yield 65 %). Analytical data matched literature.[2]

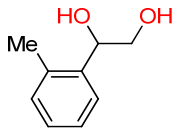
1-(3-Methylphenyl)ethane-1,2-diol **3.46**



3.46

Dihydroxylation was performed according to procedure 2 (yield 44 %). Analytical data matched literature.[2]

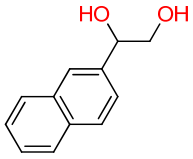
1-(2-Methylphenyl)ethane-1,2-diol **3.45**



3.45

Dihydroxylation was performed according to procedure 2 (yield 33 %). Analytical data matched literature.[2]

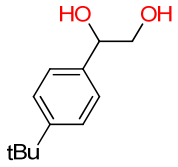
1-(4-Chlorophenyl)ethane-1,2-diol **3.38**



3.38

Dihydroxylation was performed according to procedure 2 (yield 32 %). Analytical data matched literature.[2]

1-(4-tert-Butylphenyl)ethane-1,2-diol **3.41**



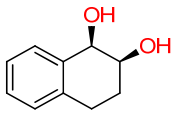
3.41

Dihydroxylation was performed according to procedure 2 (yield 66%).

R_f (Hexanes:EtOAc = 1:1) 0.30; **m.p.** 126.5-128.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.81 (dd, J = 4.0 and 8.0 Hz, 1H), 3.67-3.79 (m, 2H), 1.32 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.0, 137.5, 125.8, 125.5,

74.5, 68.0, 34.5, 31.3; **IR** *v* 3409, 2958, 1384 cm^{-1}; **HRMS** .$[M+Na+]^{+}$: 217.1204, found: 217.1200.

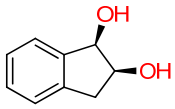
Tetrahydro naphthalene 1,2-*cis*-diol **3.49**



3.49

Dihydroxylation was performed according to procedure 2 (yield 71%). The diastereoselectivity ratio was *syn*:*anti* = 4:1. Analytical data matched literature.[4]

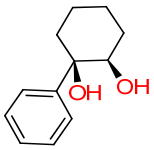
Indane-1,2 –diol **3.50**



3.50

Dihydroxylation was performed according to procedure 2 (yield 45%). The diastereoselectivity ratio was *syn*:*anti* = >25:1. Analytical data matched literature.[2]

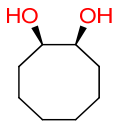
2-Phenyl-cyclohexane-1,2-diol **3.52**



3.52

Dihydroxylation was performed according to procedure 2 (yield 35%). The diastereoselectivity ratio was *syn*:*anti* = 25:1. Analytical data matched literature.[5]

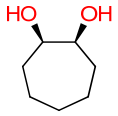
1,2-Cyclooctanediol **3.53**



3.53

Dihydroxylation was performed according to procedure 2 (yield 74%). The diastereoselectivity ratio was *syn*:*anti* = 25:1. Analytical data matched literature.[6]

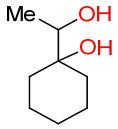
1,2-Cycloheptanediol **3.54**



3.54

Dihydroxylation was performed according to procedure 2 (yield 44%). The diastereoselectivity ratio was *syn*:*anti* = 25:1. Analytical data matched literature.[6]

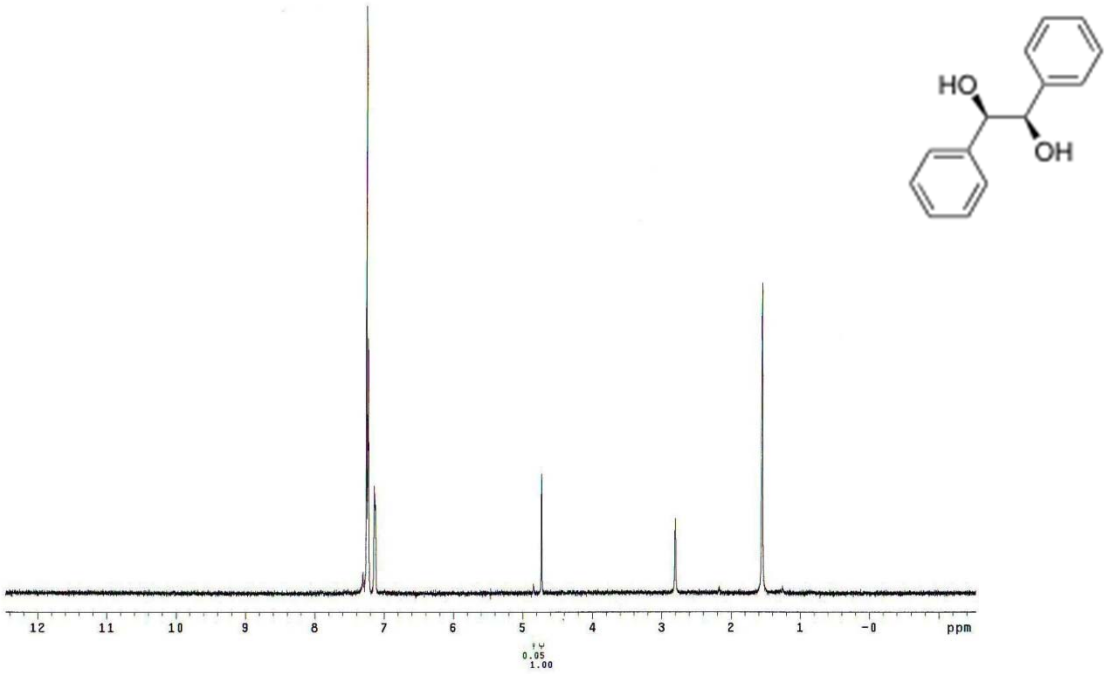
1-(1-Hydroxyethyl)cyclohexanol **3.51**

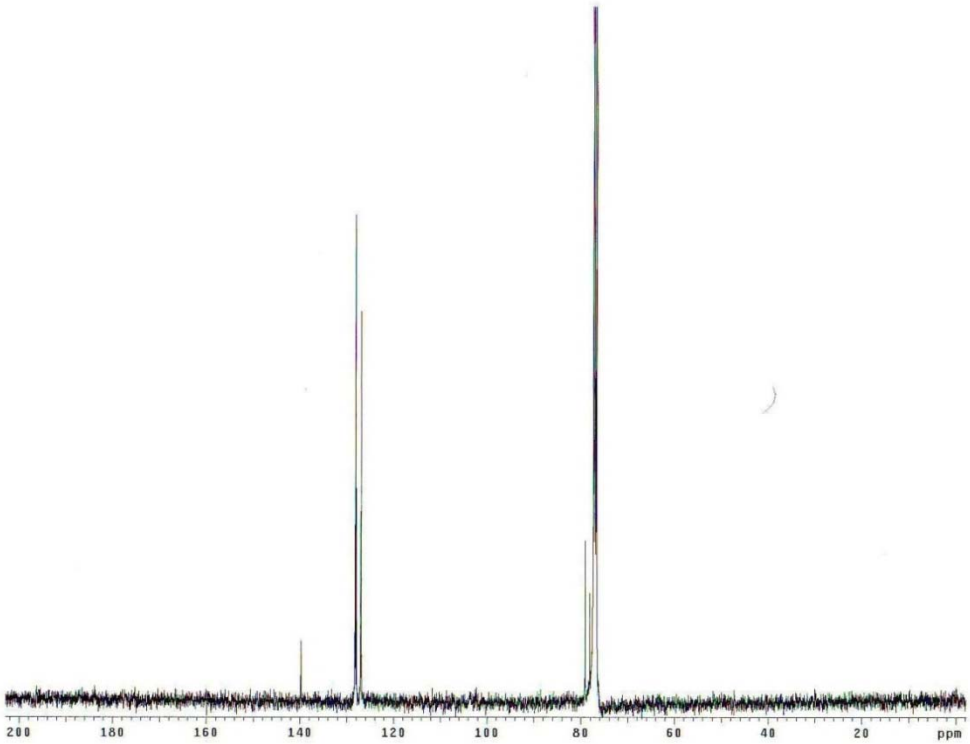


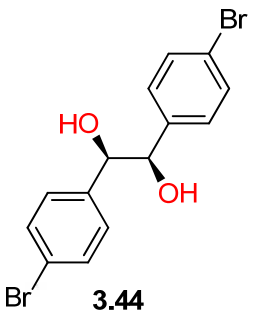
3.51

Dihydroxylation was performed according to procedure 2 (yield 67%). The diastereoselectivity ratio was *syn*:*anti* = 25:1. Analytical data matched literature.[2]

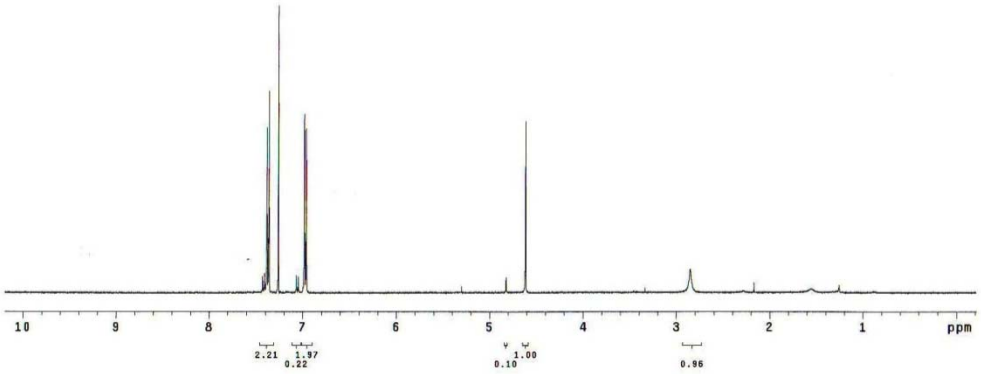
3.7 Spectrum:

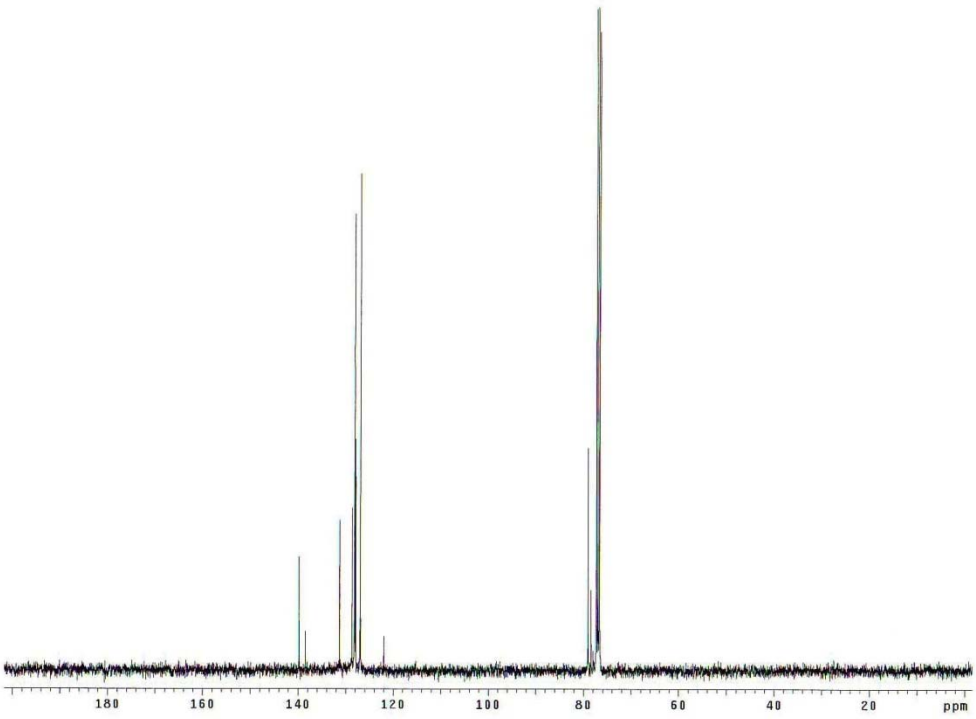

HO
OH
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
0.05
1.00

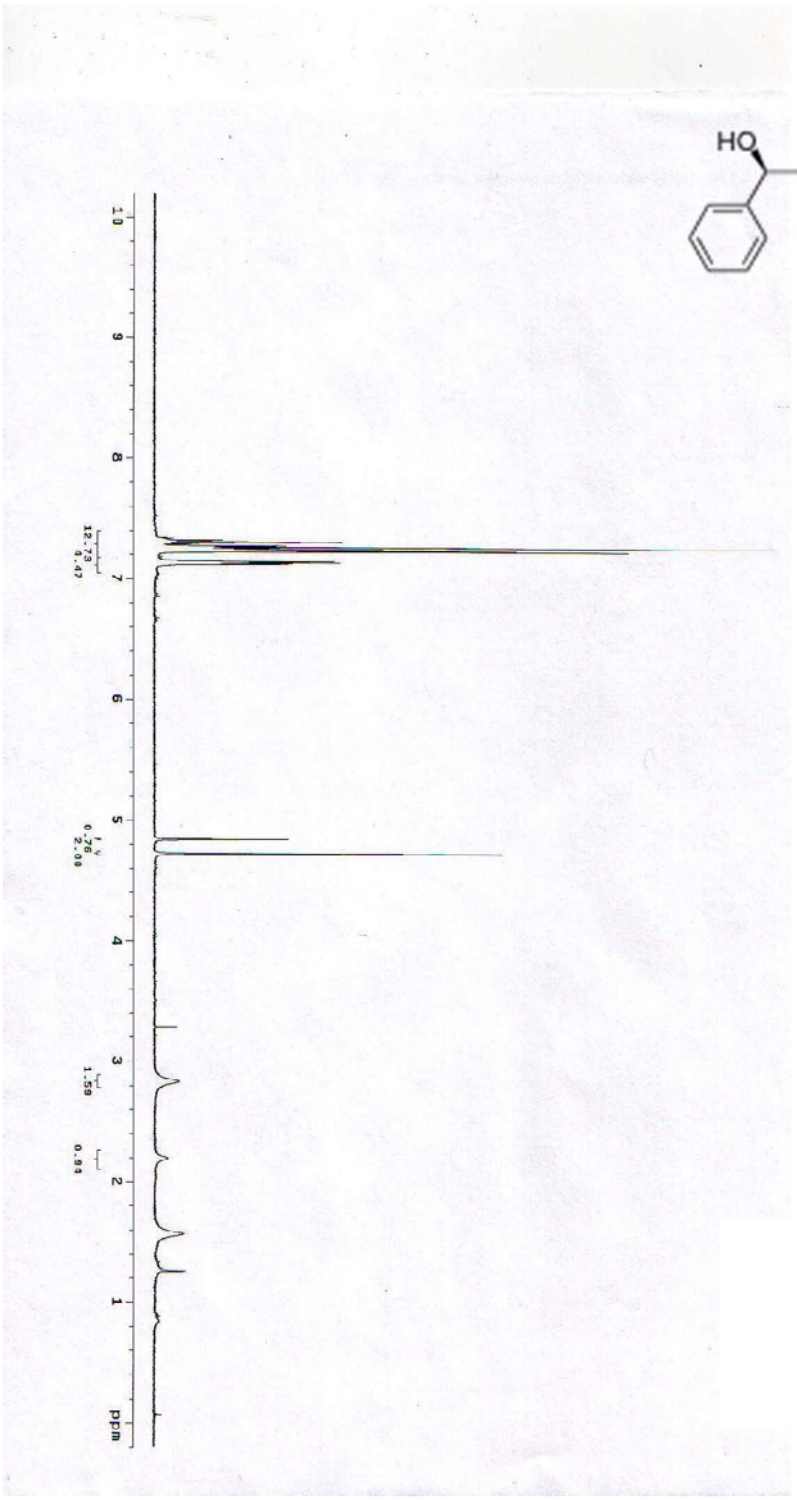

200
180
160
140
120
100
80
60
40
20
ppm

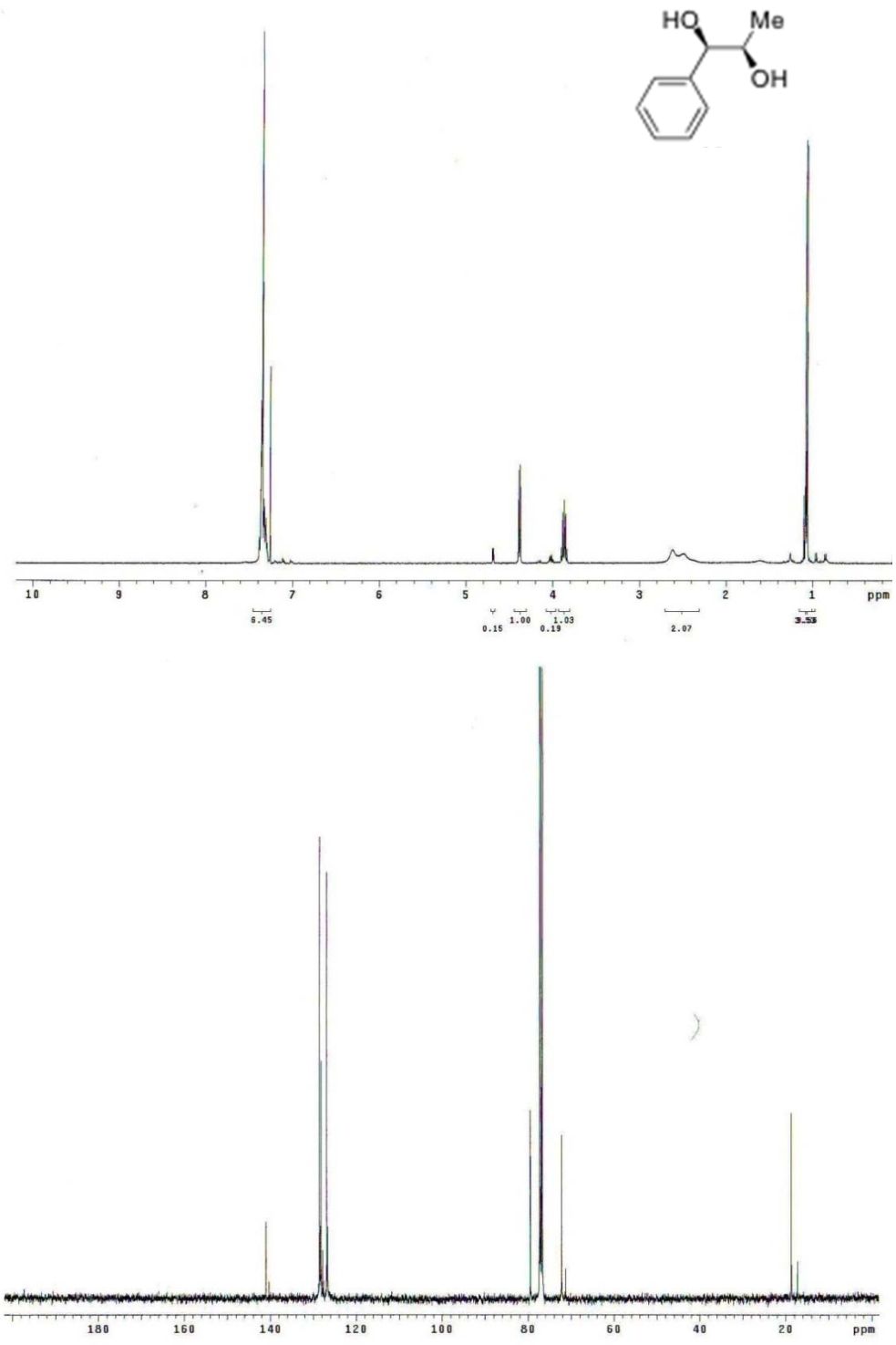

Br
HO
OH
Br

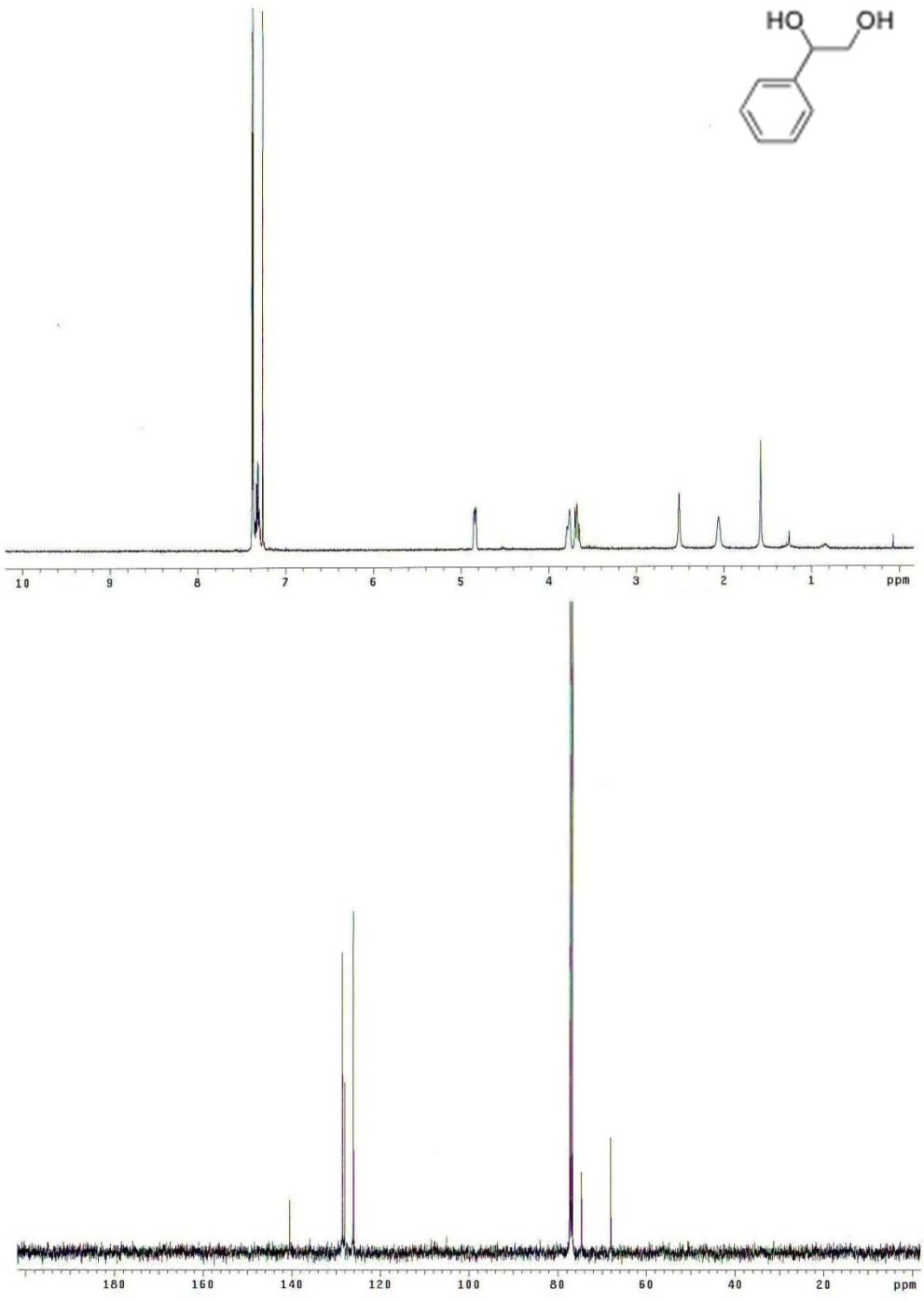
3.44

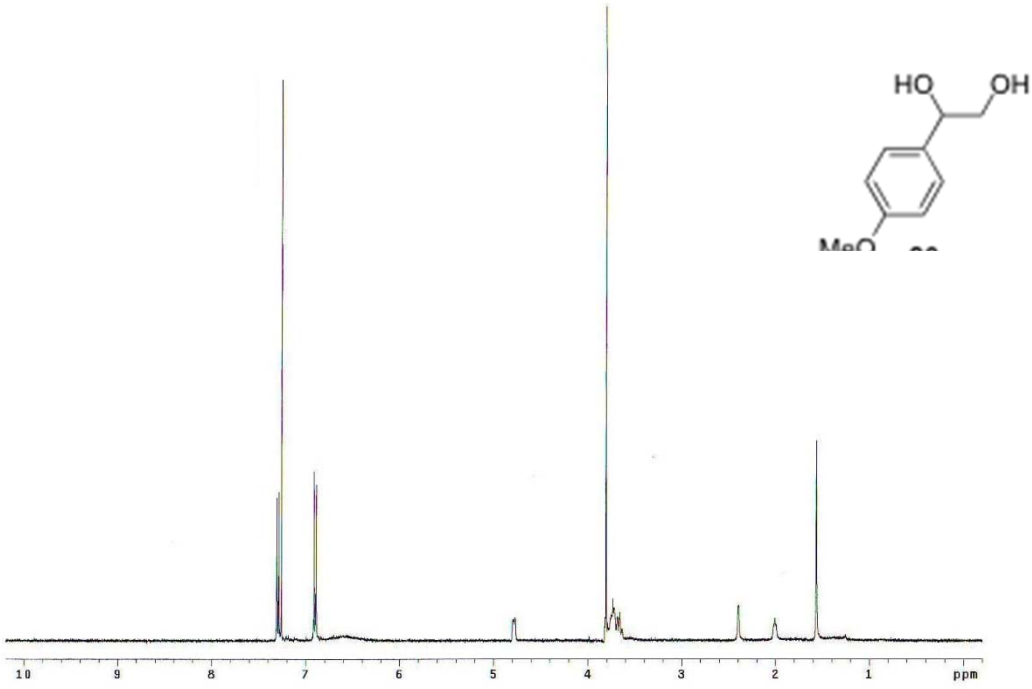

10
9
8
7
6
5
4
3
2
1
ppm
2.21
1.97
0.22
1.00
0.10
0.96

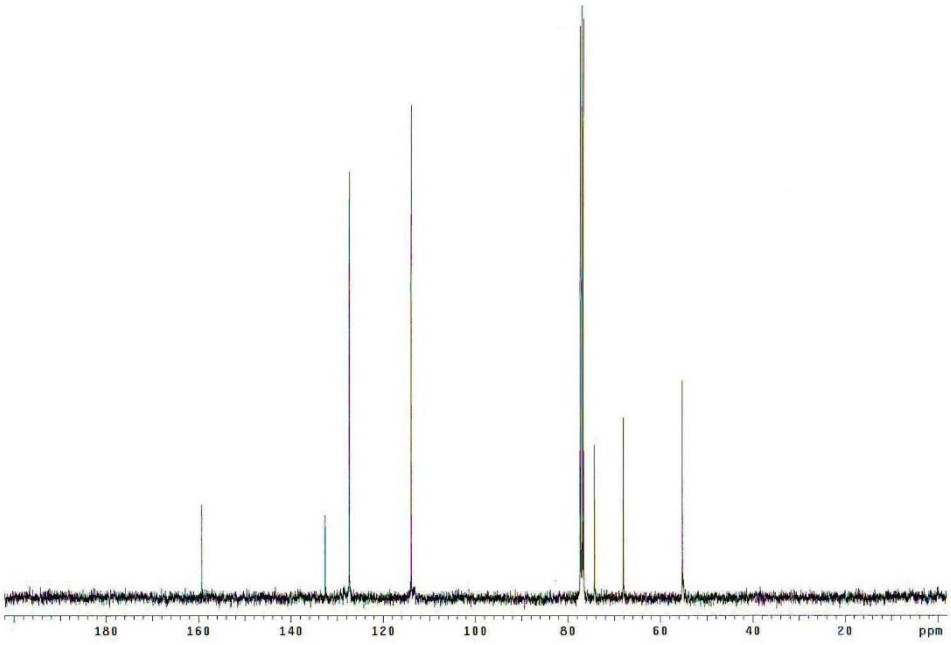

180
160
140
120
100
80
60
40
20
ppm

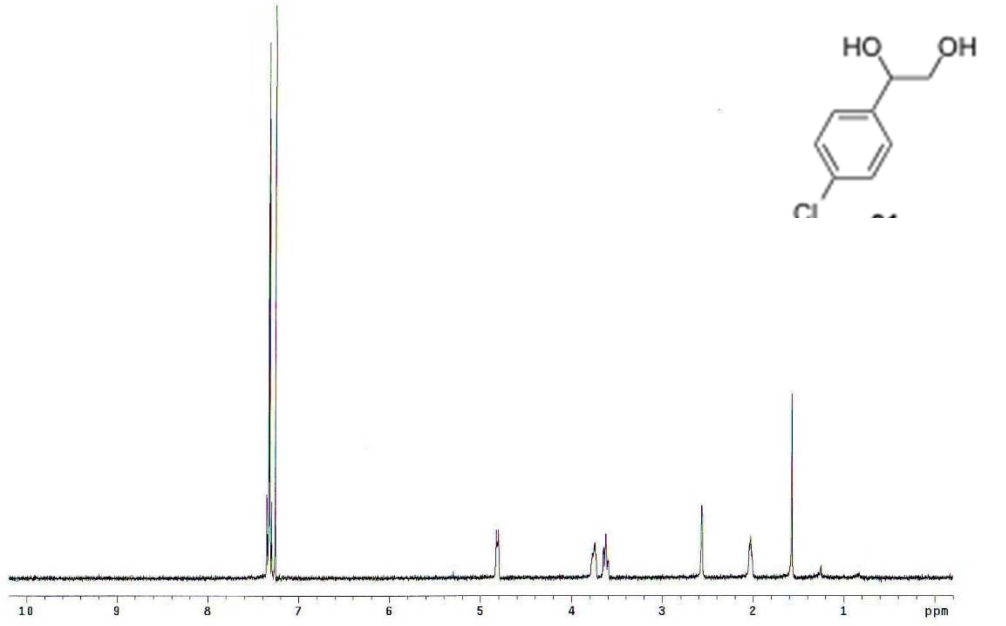

HO
OH
10
9
8
7
6
5
4
3
2
1
ppm
12.73
4.47
0.76
2.00
1.59
0.94

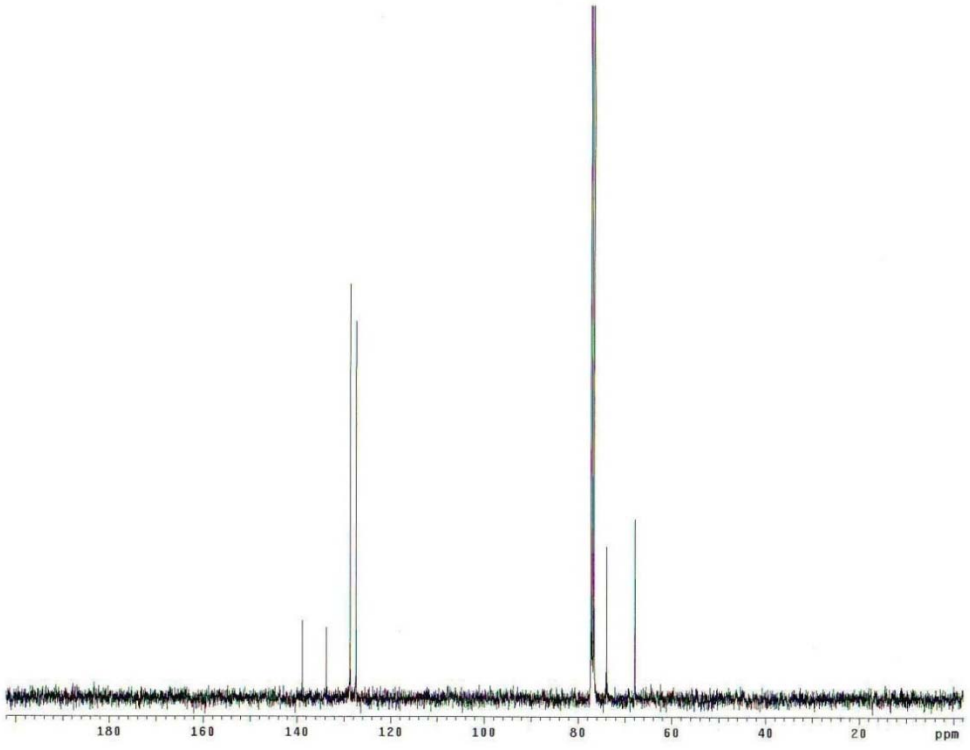

HO
Me
OH
10
9
8
7
6
5
4
3
2
1
ppm
6.45
0.15
1.00
0.19
1.03
2.07
180
160
140
120
100
80
60
40
20
ppm

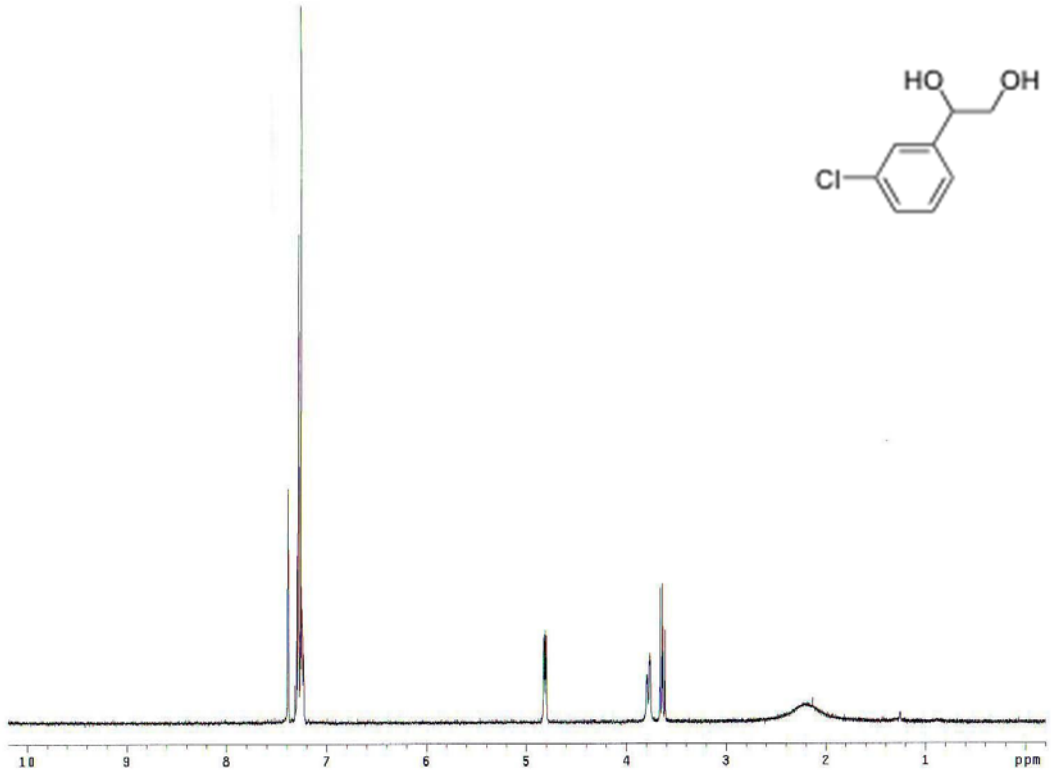

HO
OH
10
9
8
7
6
5
4
3
2
1
ppm
180
160
140
120
100
80
60
40
20
ppm

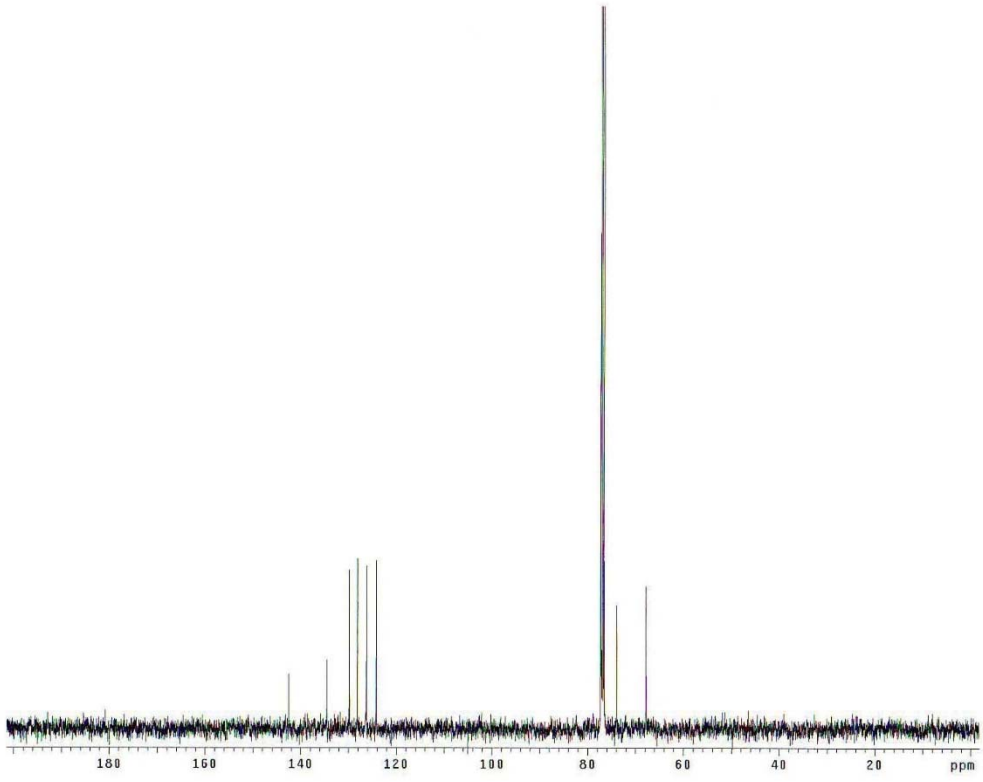

HO
OH
10
9
8
7
6
5
4
3
2
1
ppm

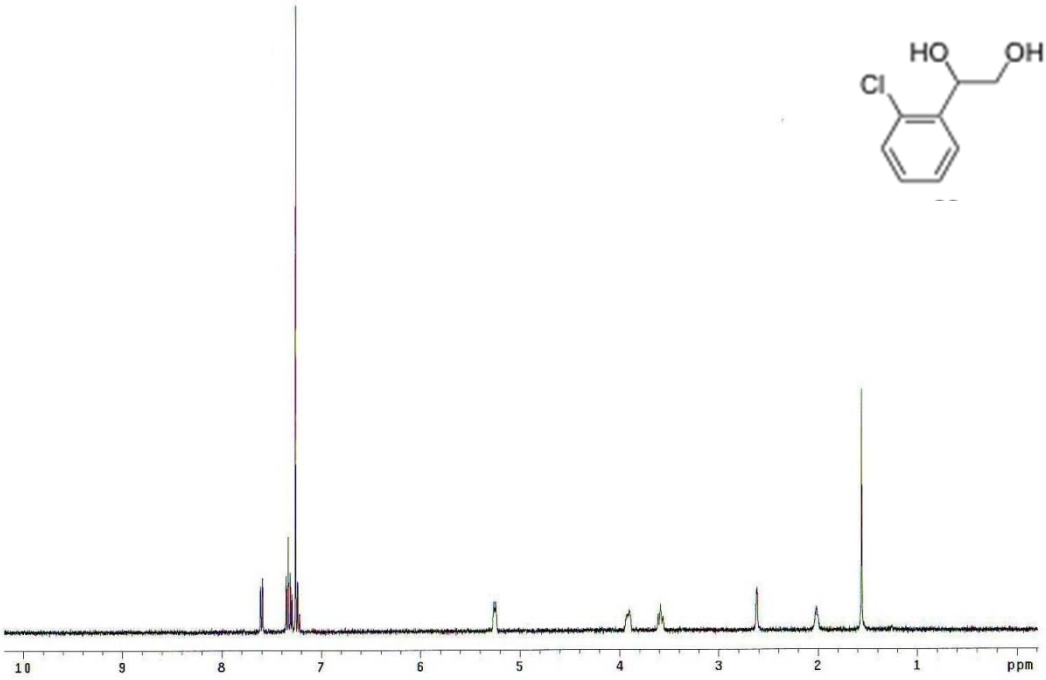

180
160
140
120
100
80
60
40
20
ppm

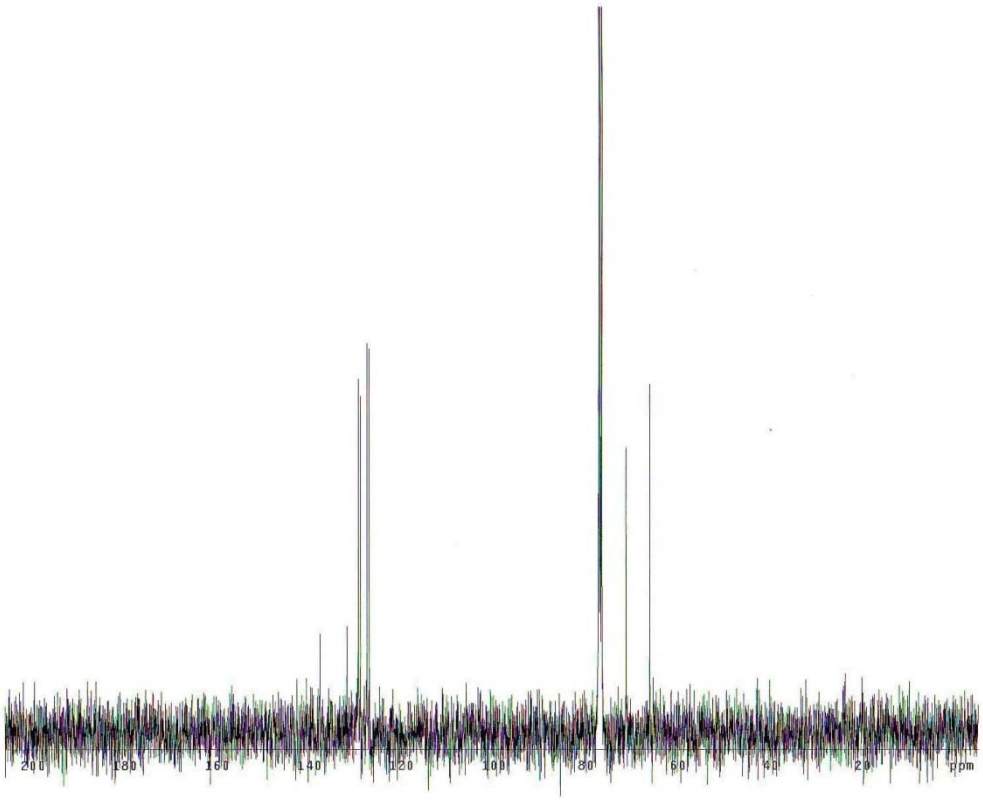

HO
OH
Cl
10
9
8
7
6
5
4
3
2
1
ppm

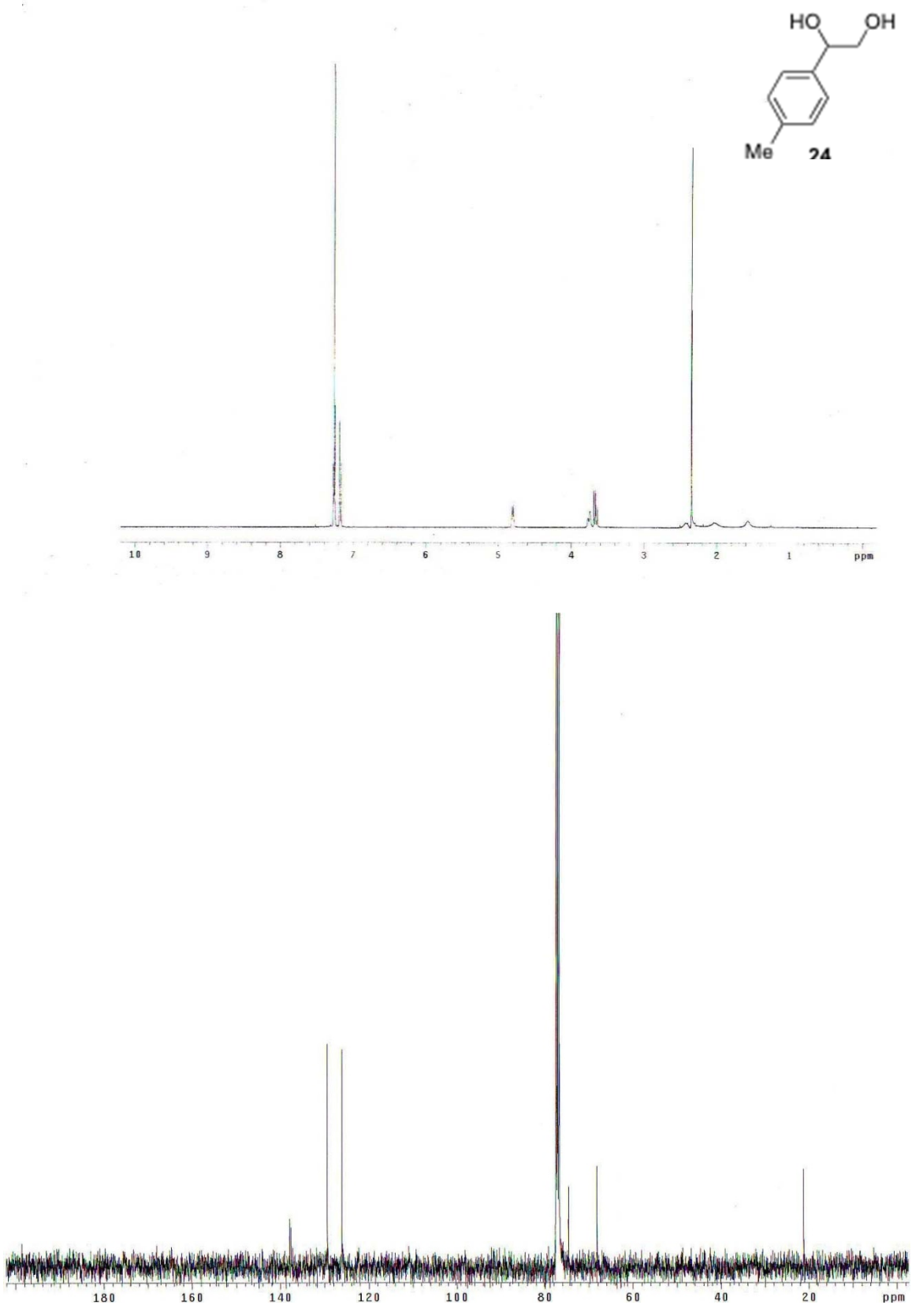

180
160
140
120
100
80
60
40
20
ppm

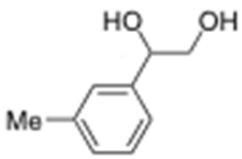

HO
OH
Cl
10
9
8
7
6
5
4
3
2
1
ppm

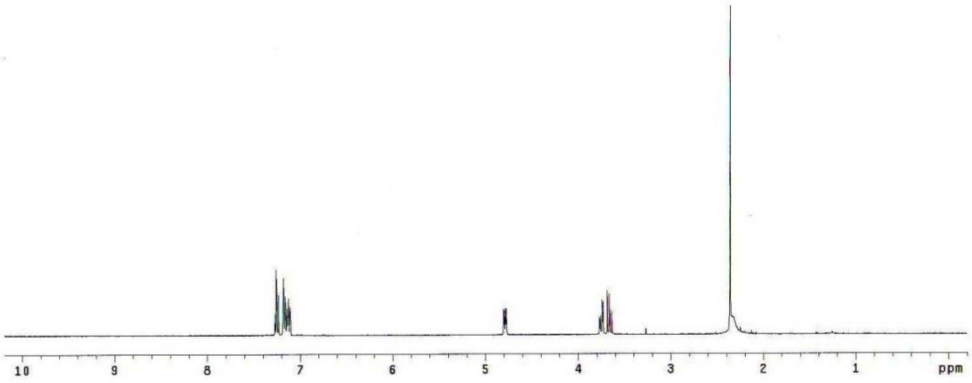

180
160
140
120
100
80
60
40
20
ppm

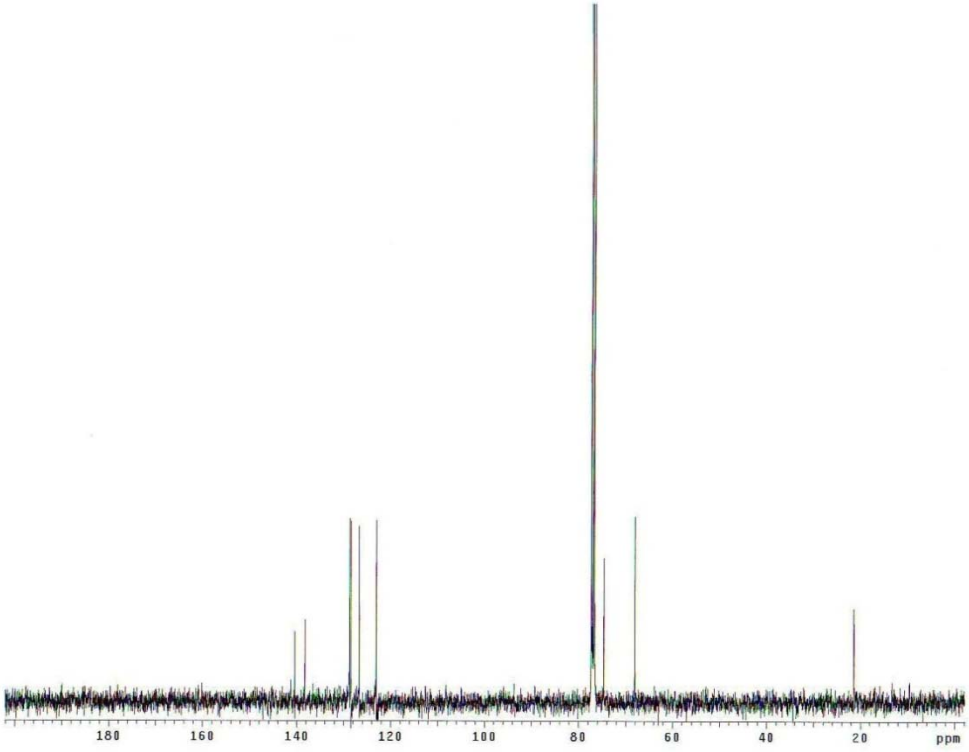

HO
OH
Cl
10
9
8
7
6
5
4
3
2
1
ppm

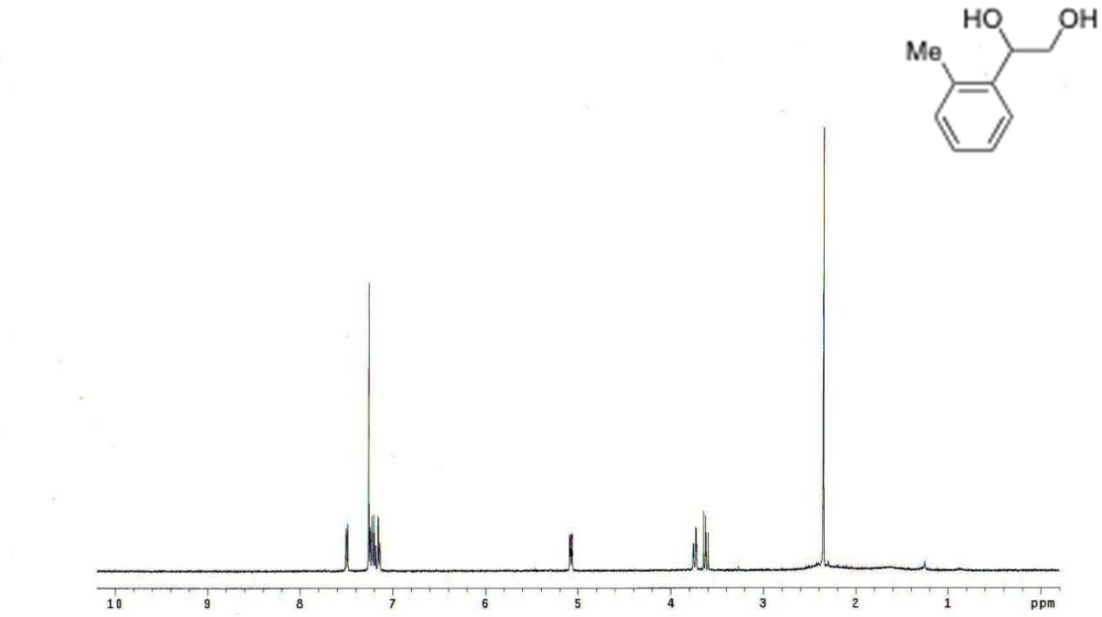

200
180
160
140
120
100
80
60
40
20
ppm

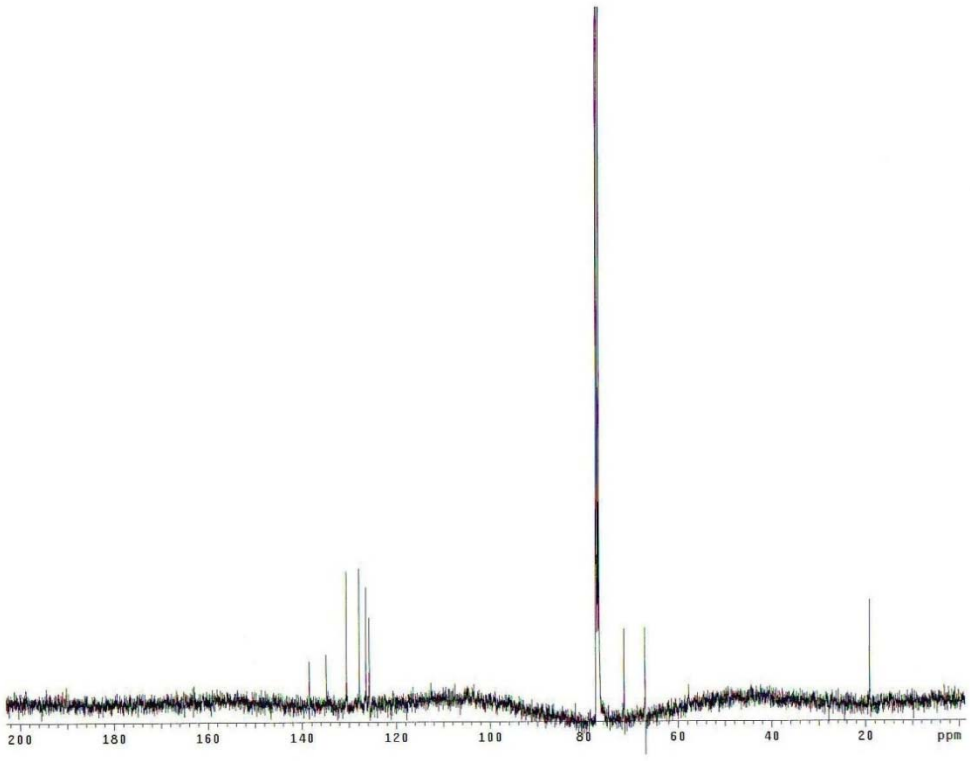

HO
OH
Me
24
10
9
8
7
6
5
4
3
2
1
ppm
180
160
140
120
100
80
60
40
20
ppm

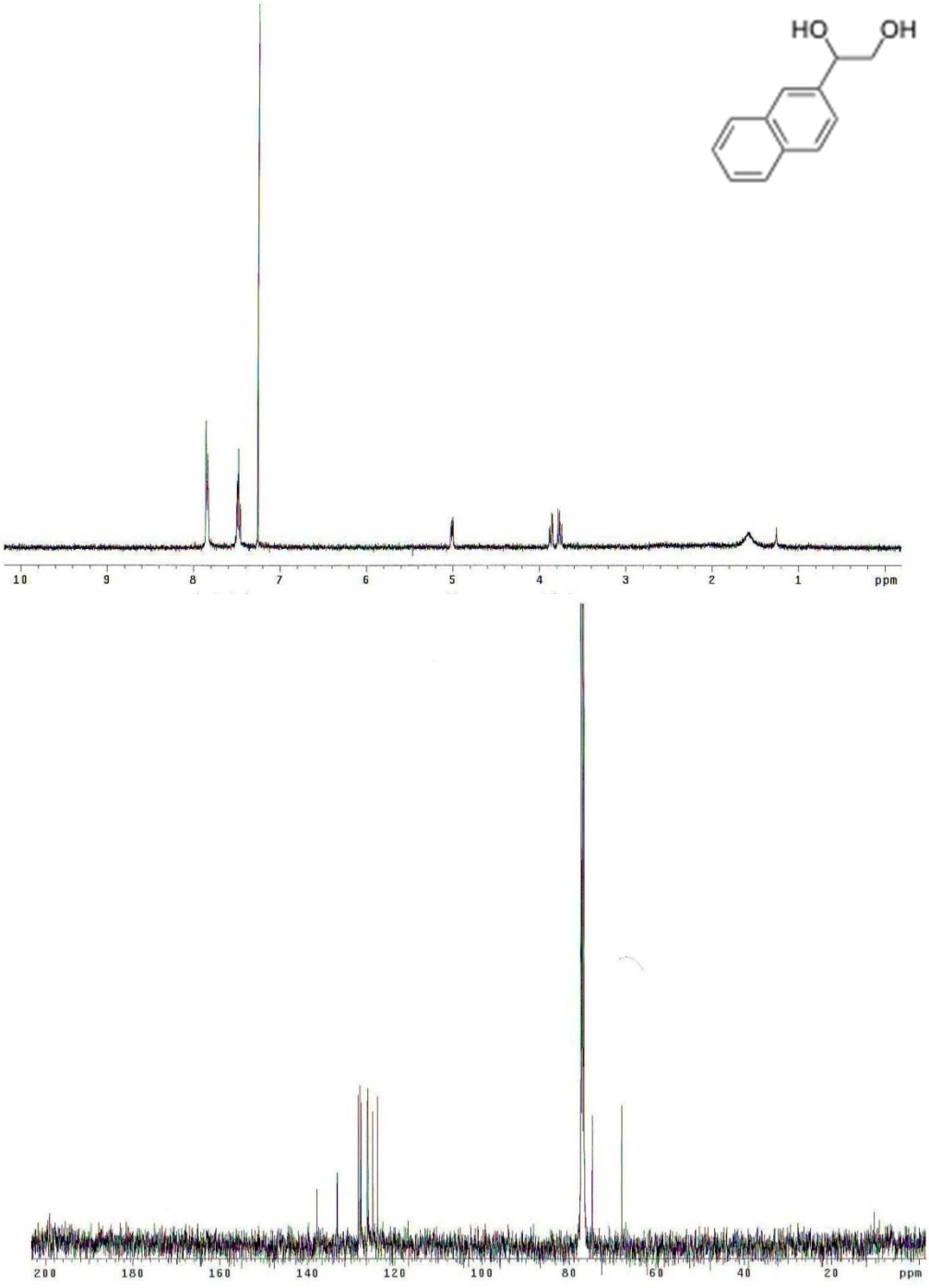

HO
OH
Me

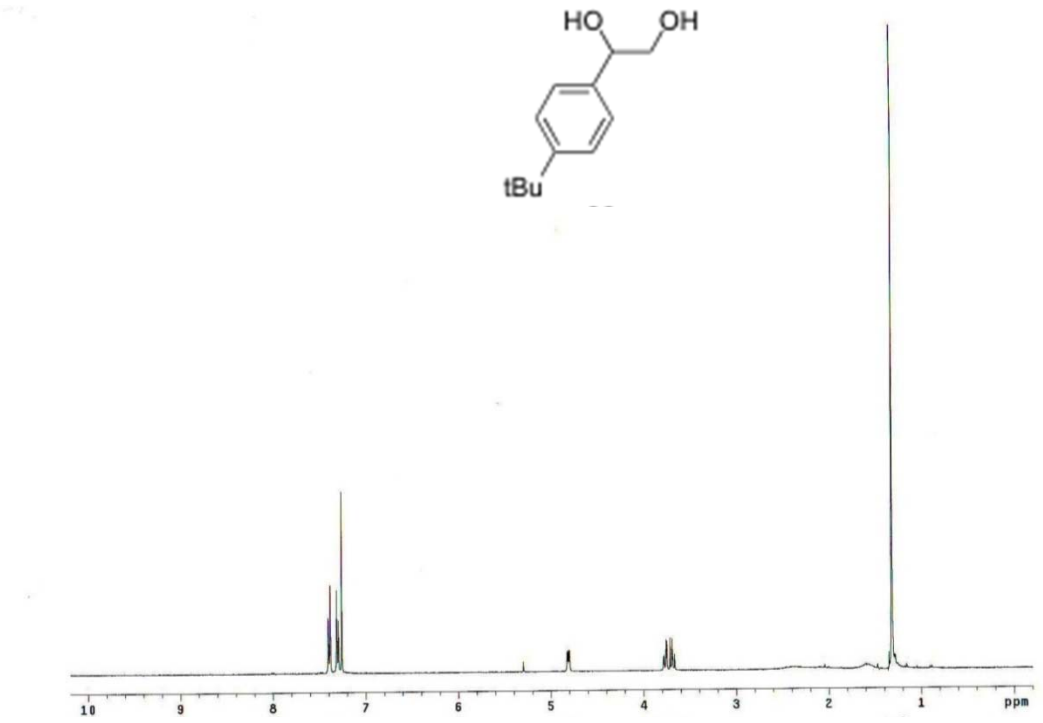

10
9
8
7
6
5
4
3
2
1
ppm

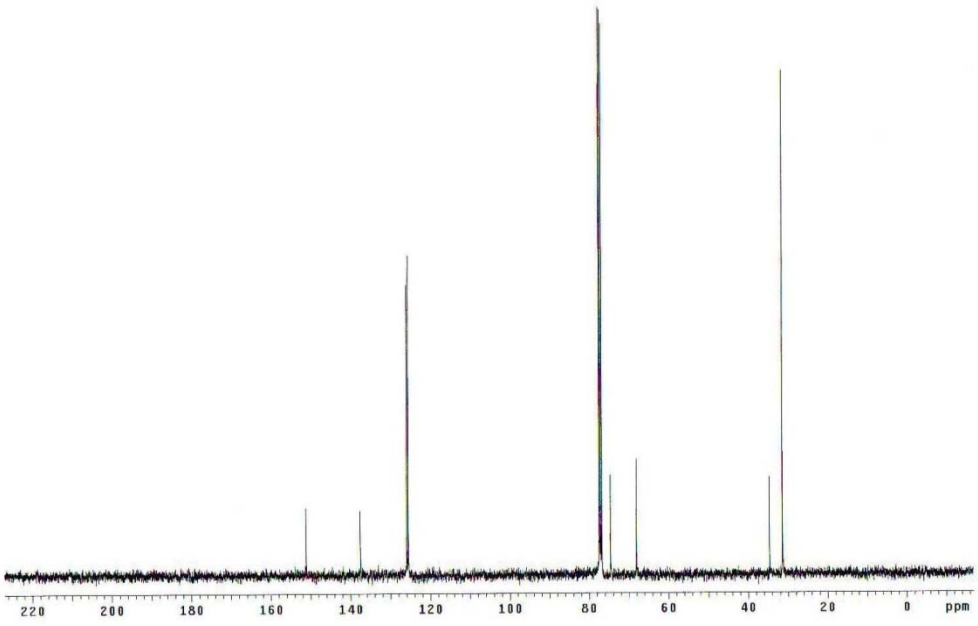

180
160
140
120
100
80
60
40
20
ppm

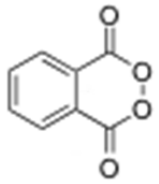

HO
OH
Me
10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

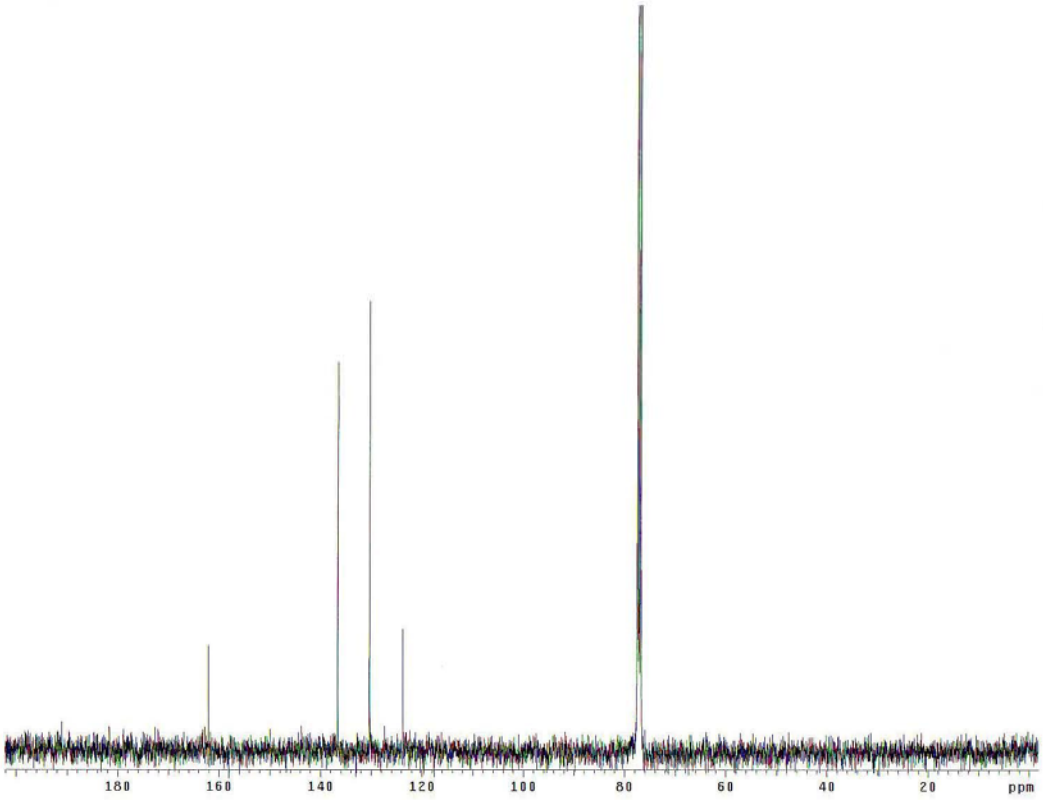

HO
OH
10
9
8
7
6
5
4
3
2
1
ppm
200
180
160
140
120
100
80
60
40
20
ppm

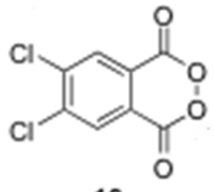

HO
OH
tBu
10
9
8
7
6
5
4
3
2
1
ppm

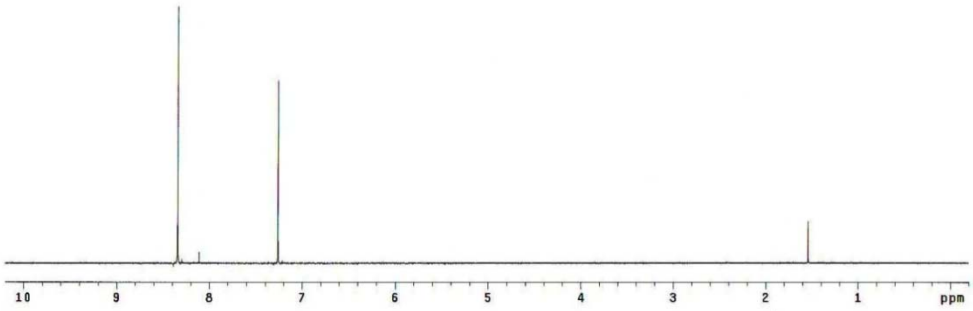

220
200
180
160
140
120
100
80
60
40
20
0
ppm

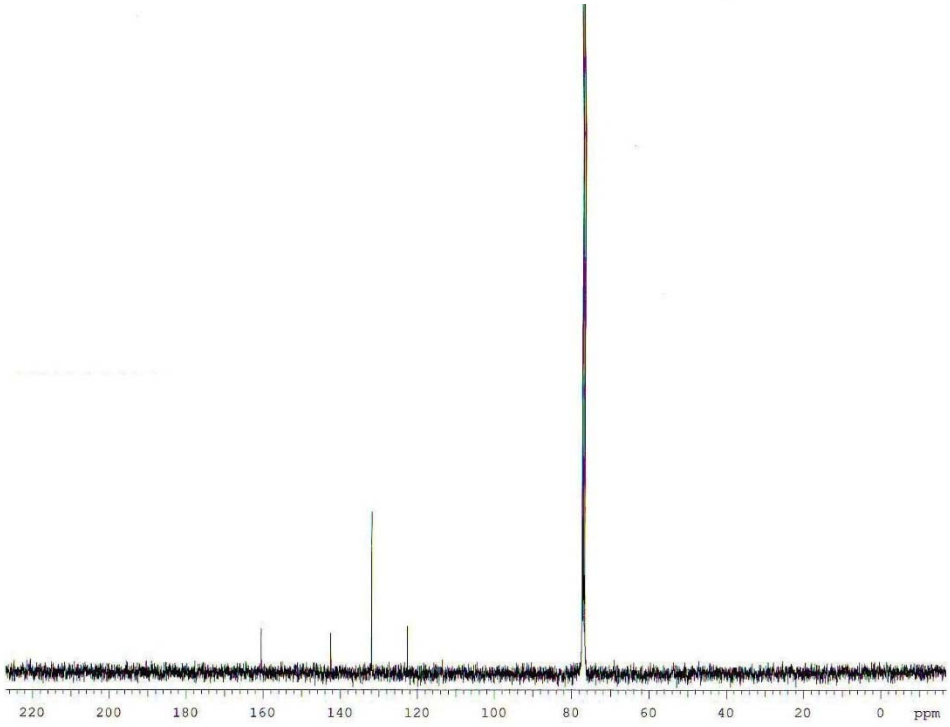


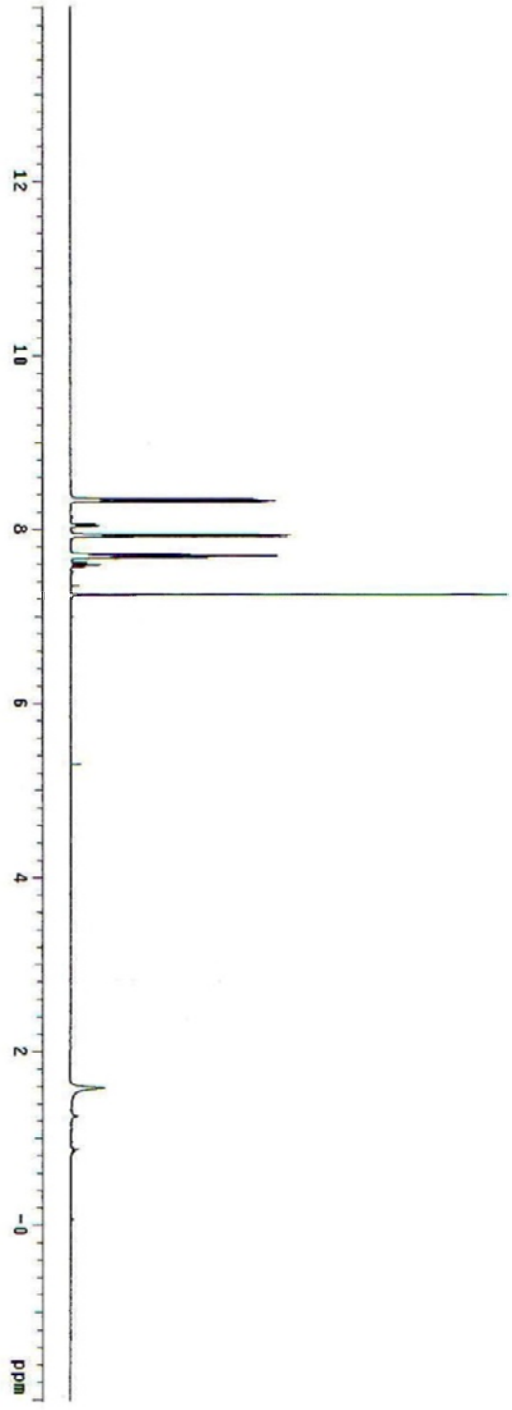
10
9
8
7
6
5
4
3
2
1
ppm

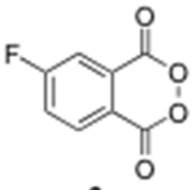

180
160
140
120
100
80
60
40
20
ppm

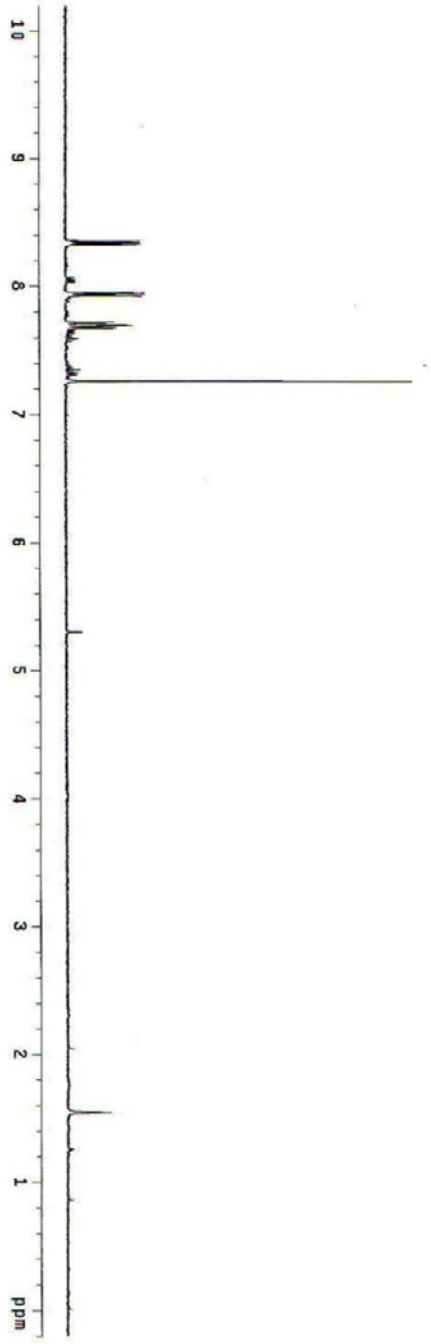

Cl
Cl
O
O
O
O

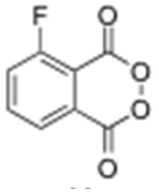

10
9
8
7
6
5
4
3
2
1
ppm

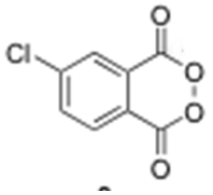

220
200
180
160
140
120
100
80
60
40
20
0
ppm

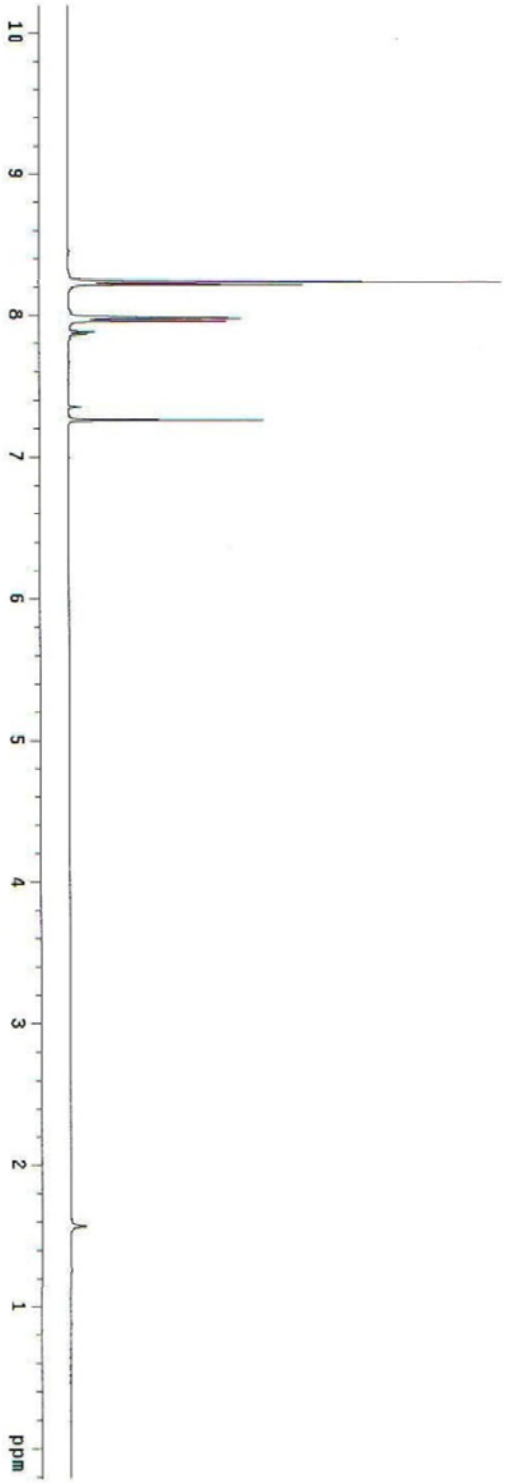

12
10
8
6
4
2
-0
ppm

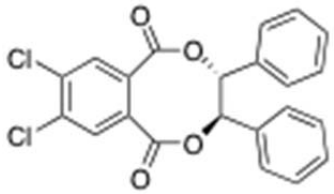

F
O
O
O
O

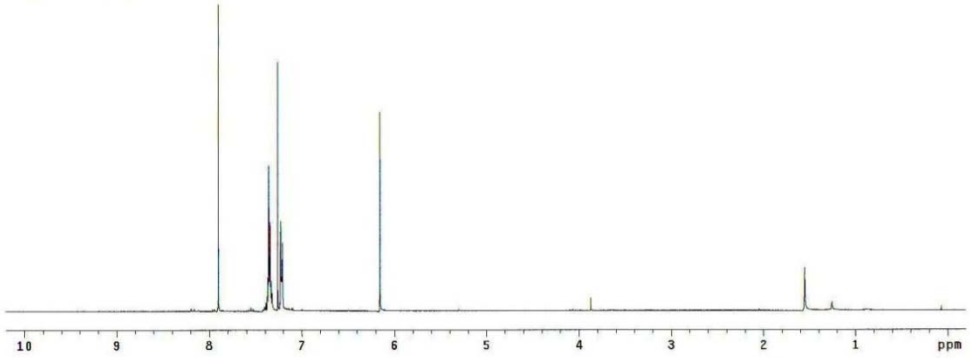

10
9
8
7
6
5
4
3
2
1
ppm

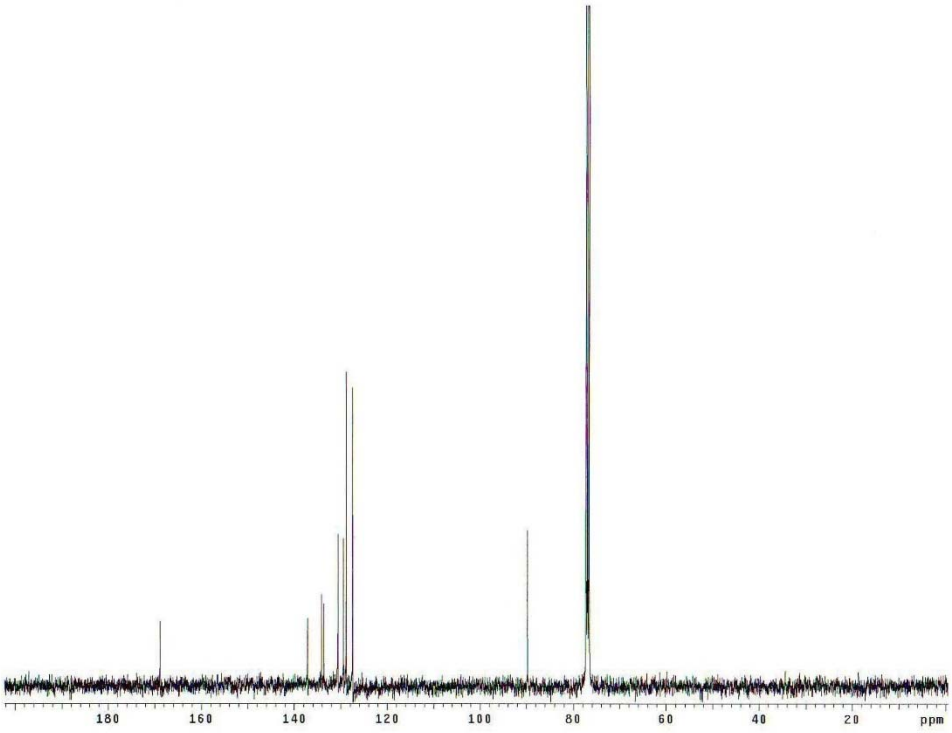

F
O
O
O
O
O

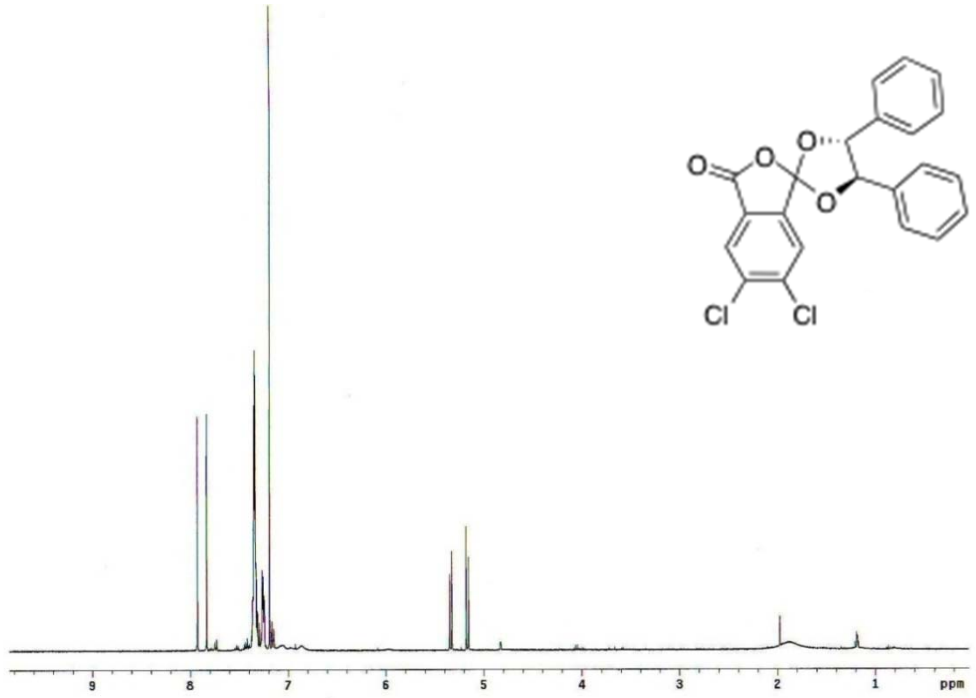

Cl
O
O
O
O

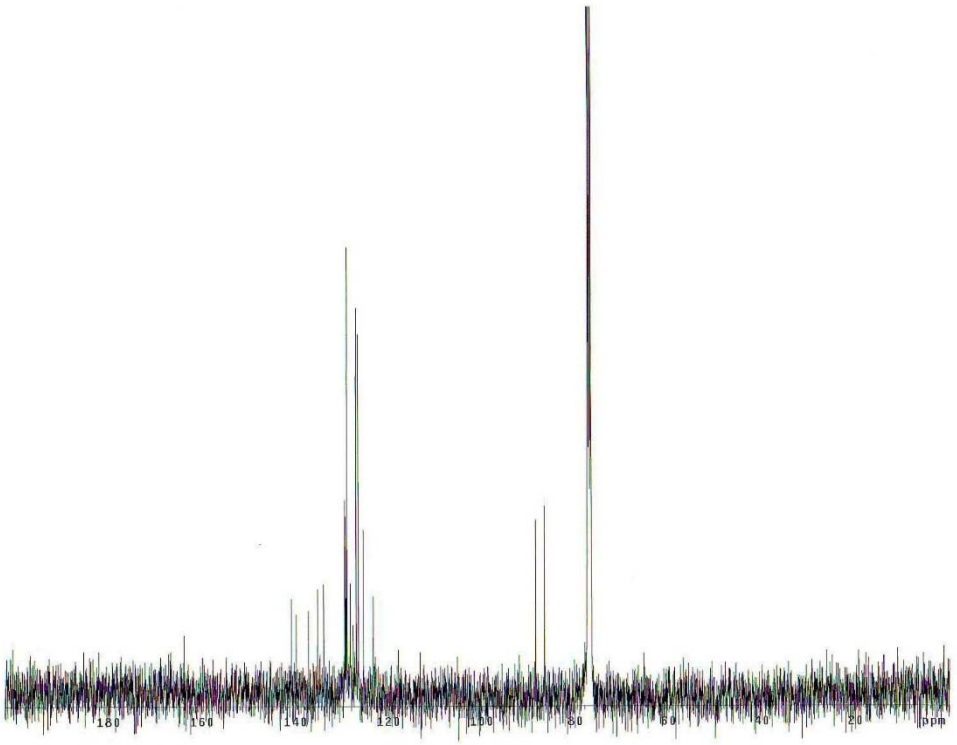

10
9
8
7
6
5
4
3
2
1
ppm

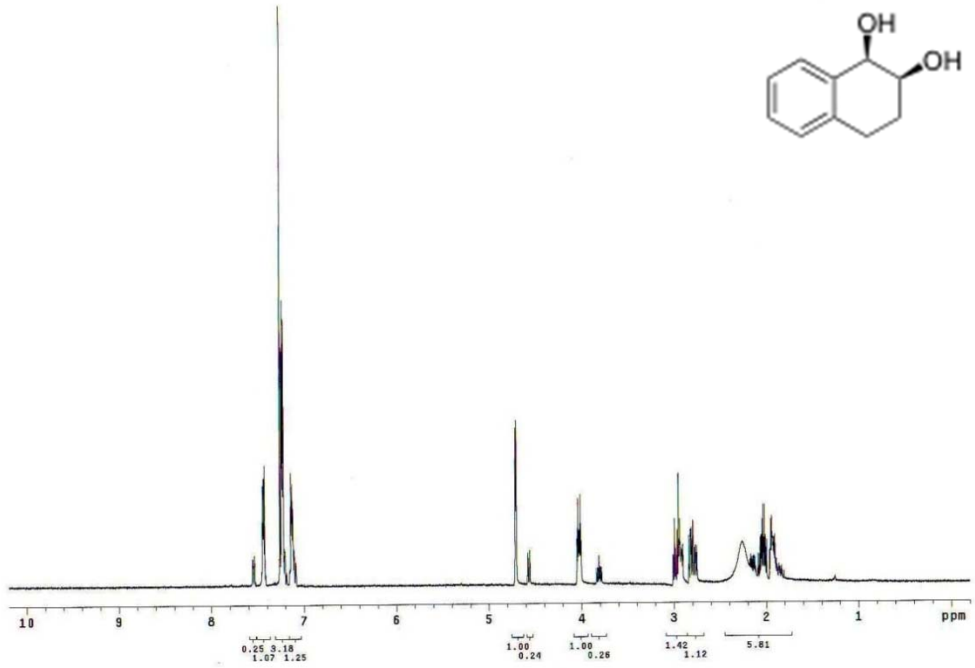

O
Cl
O
Cl
O
O

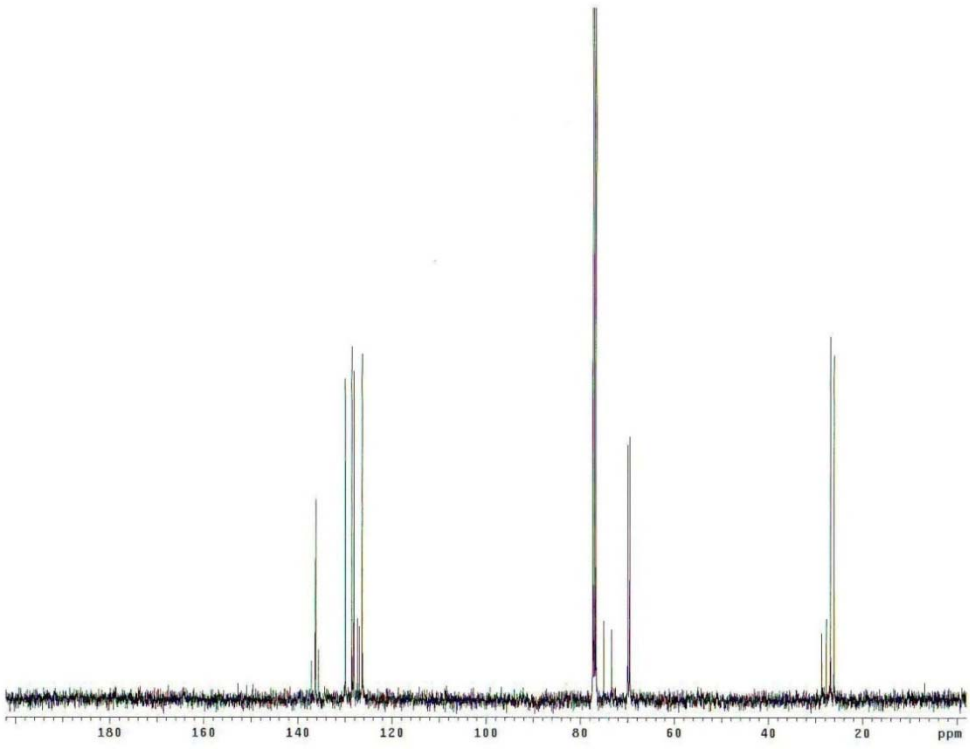

10
9
8
7
6
5
4
3
2
1
ppm

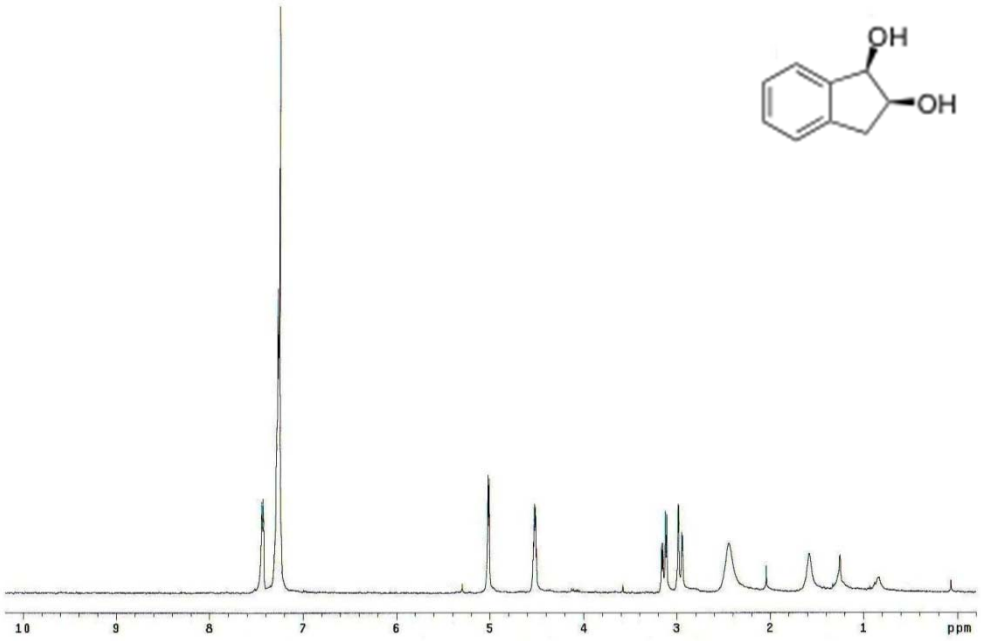

180
160
140
120
100
80
60
40
20
ppm


O
O
O
O
Cl
Cl
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm


OH
OH
10
9
8
7
6
5
4
3
2
1
ppm
0.25 3.18
1.07 1.25
1.00
0.24
1.00
0.26
1.42
1.12
5.81


180
160
140
120
100
80
60
40
20
ppm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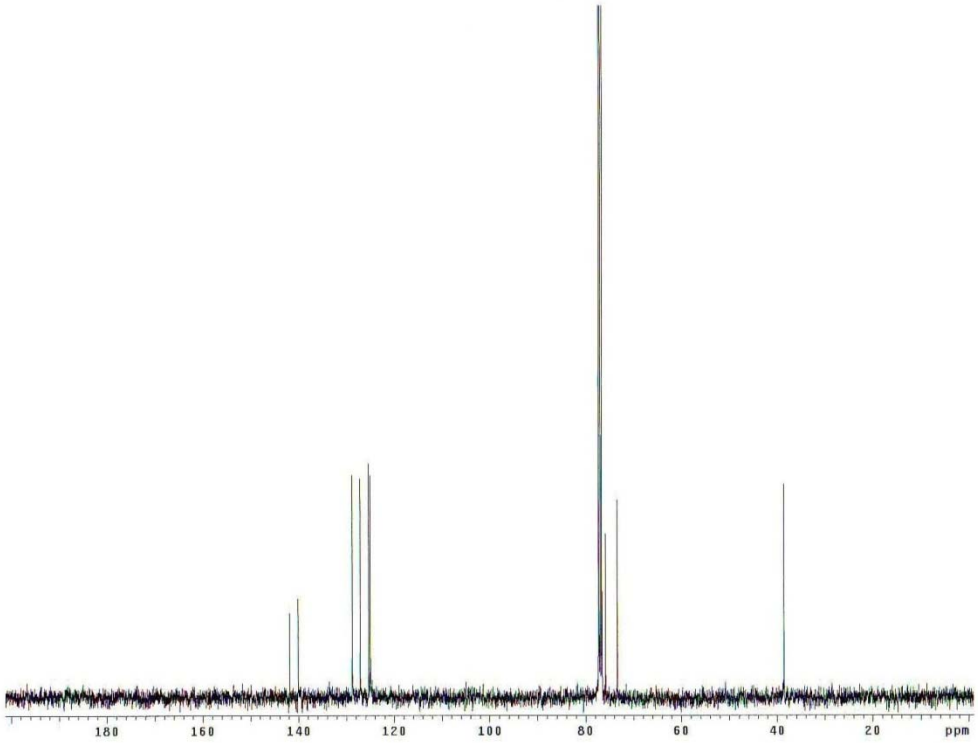
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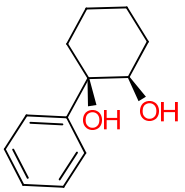
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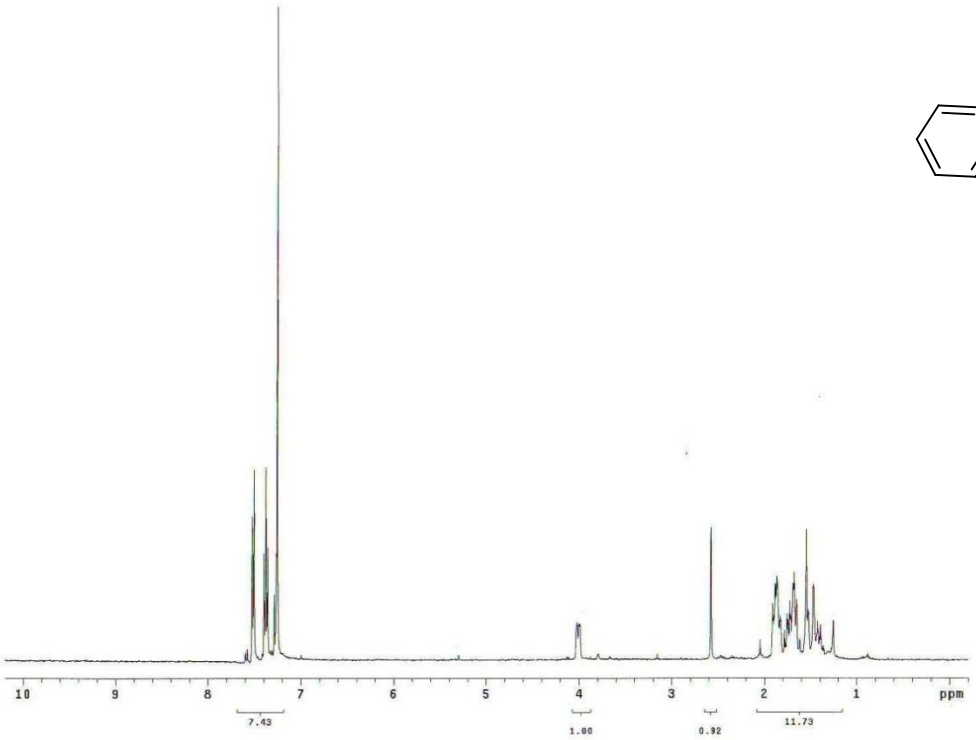
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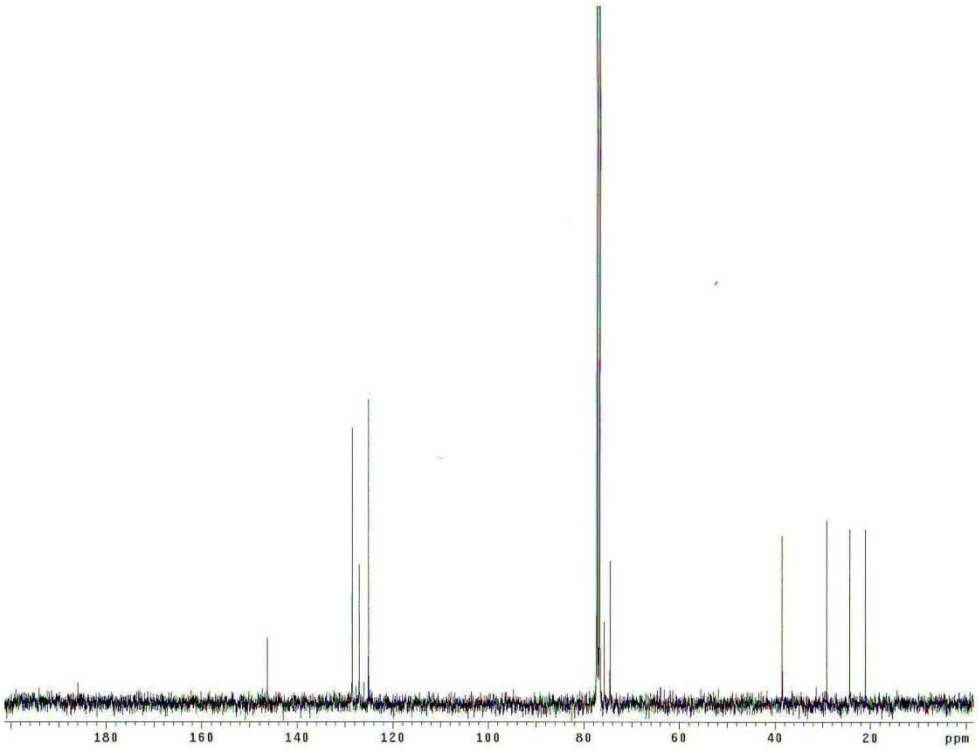
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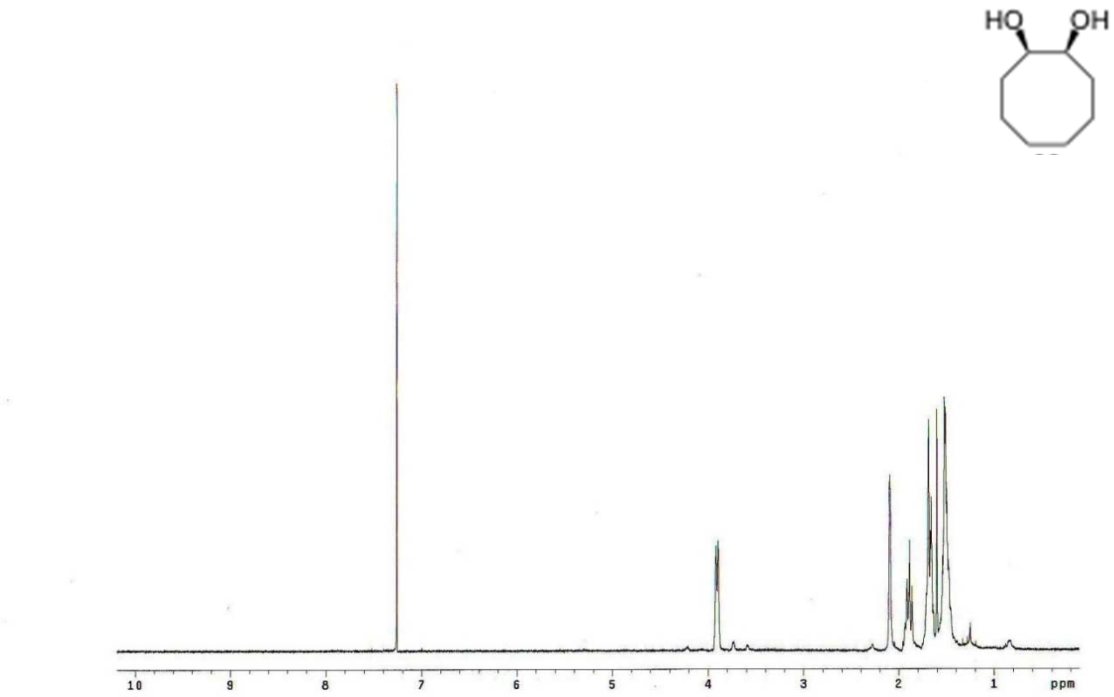
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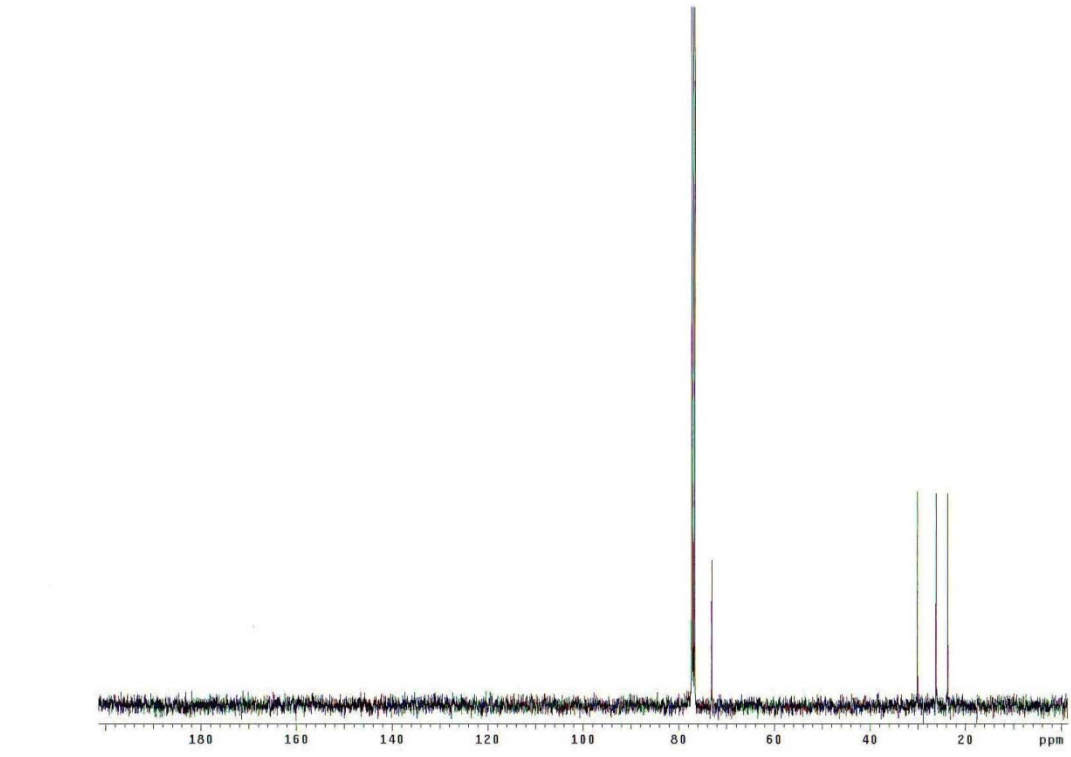
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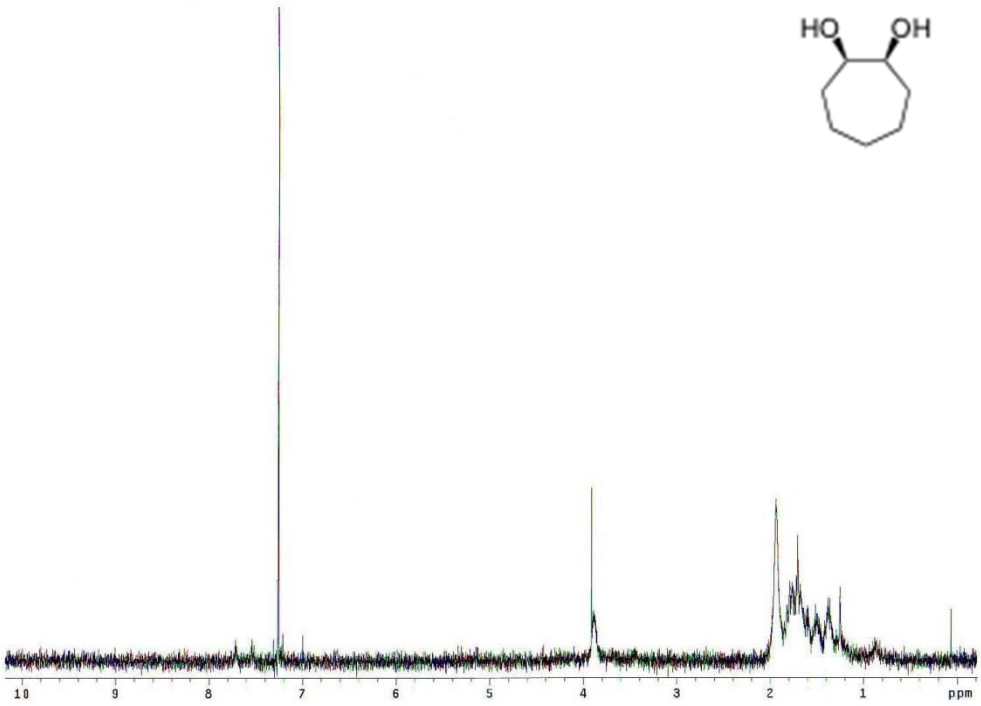
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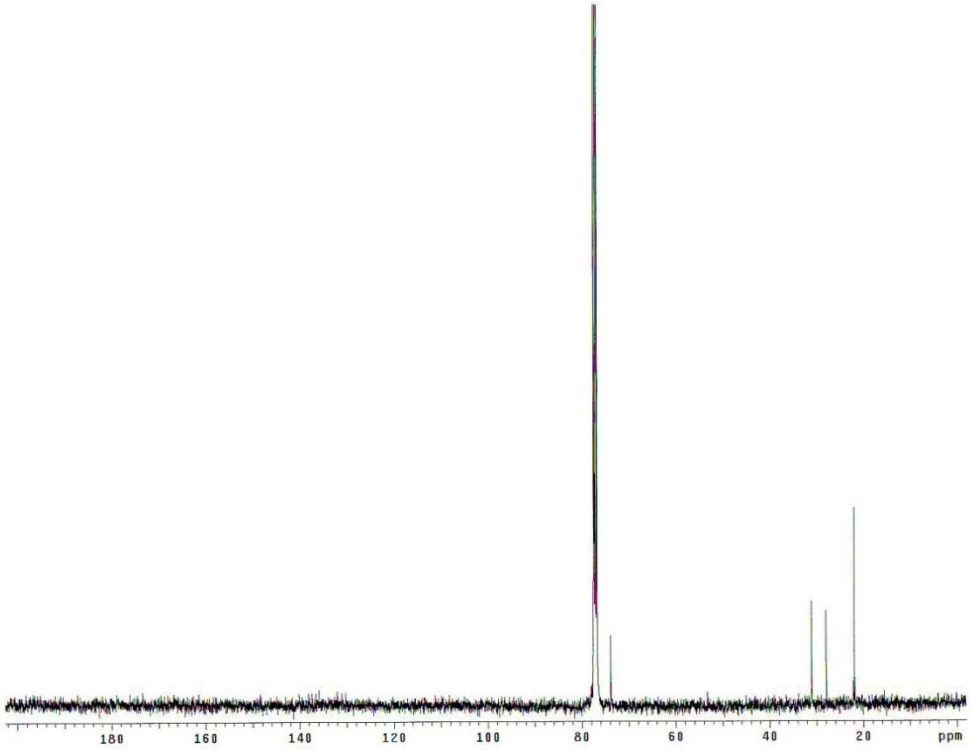
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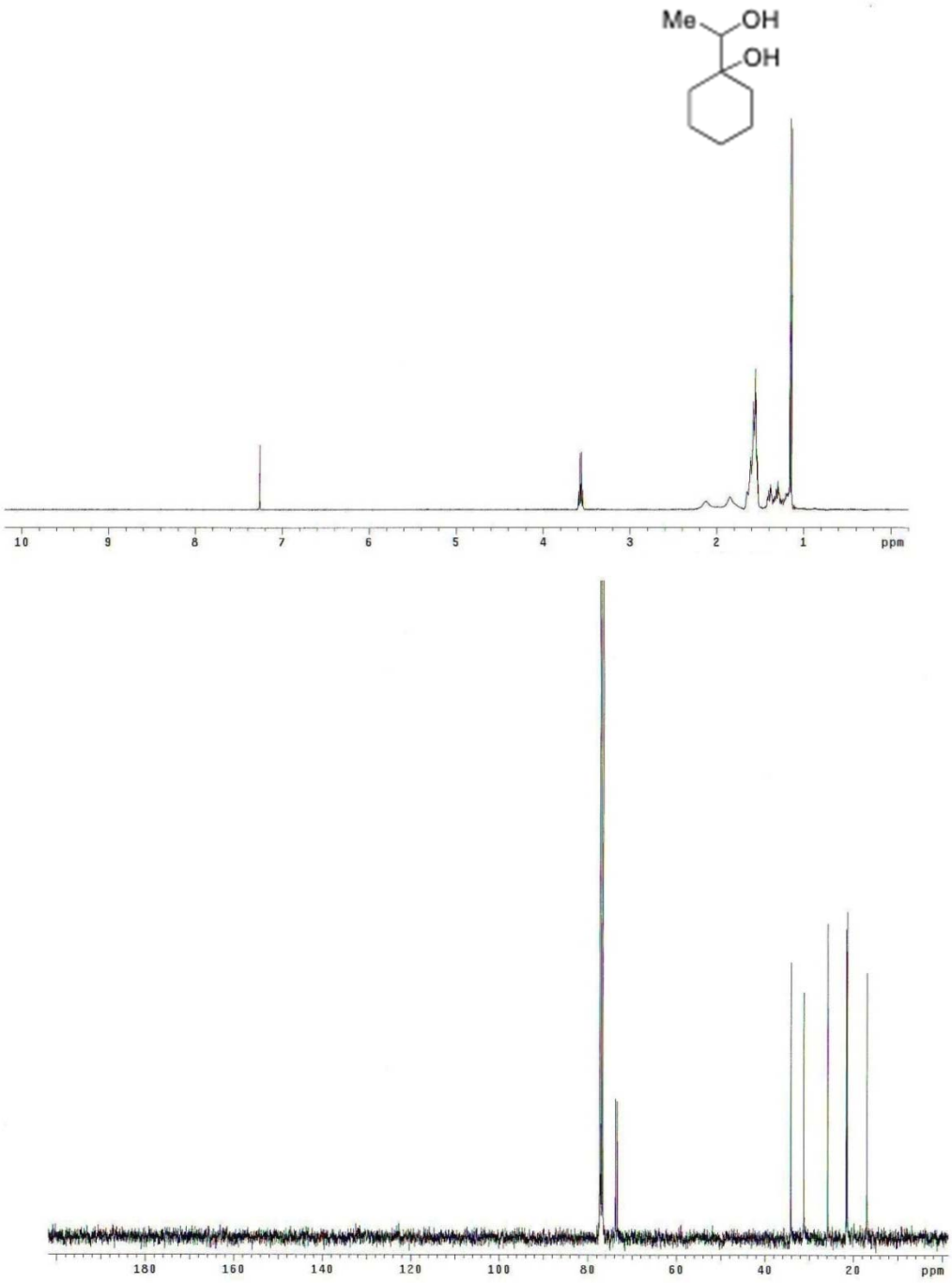
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References for Experimental 3.7 and Spectra 3.8:

(1) Greene, F. D.; John, K. *J. Org. Chem.* **1968**, *28*, 2168.

(2) Griffith, J. C.; Jones, K. M.; Coe, D. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem.Soc.* **2010**, *132*, 14409.

(3) Hudlicky, T.; Boros, E. E; Boros, C. H. *Tetrahedron: Assymmetry* **1993**, *4*, 1365.

(3) Wang, A.; Jiang, H. *J. Org. Chem.* **2010**, *75*, 2321.

(4) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2370.

(5) Nagayama,, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.

CHAPTER 4 Phthaloyl Peroxide-Mediated Hydroxylation of Arenes.

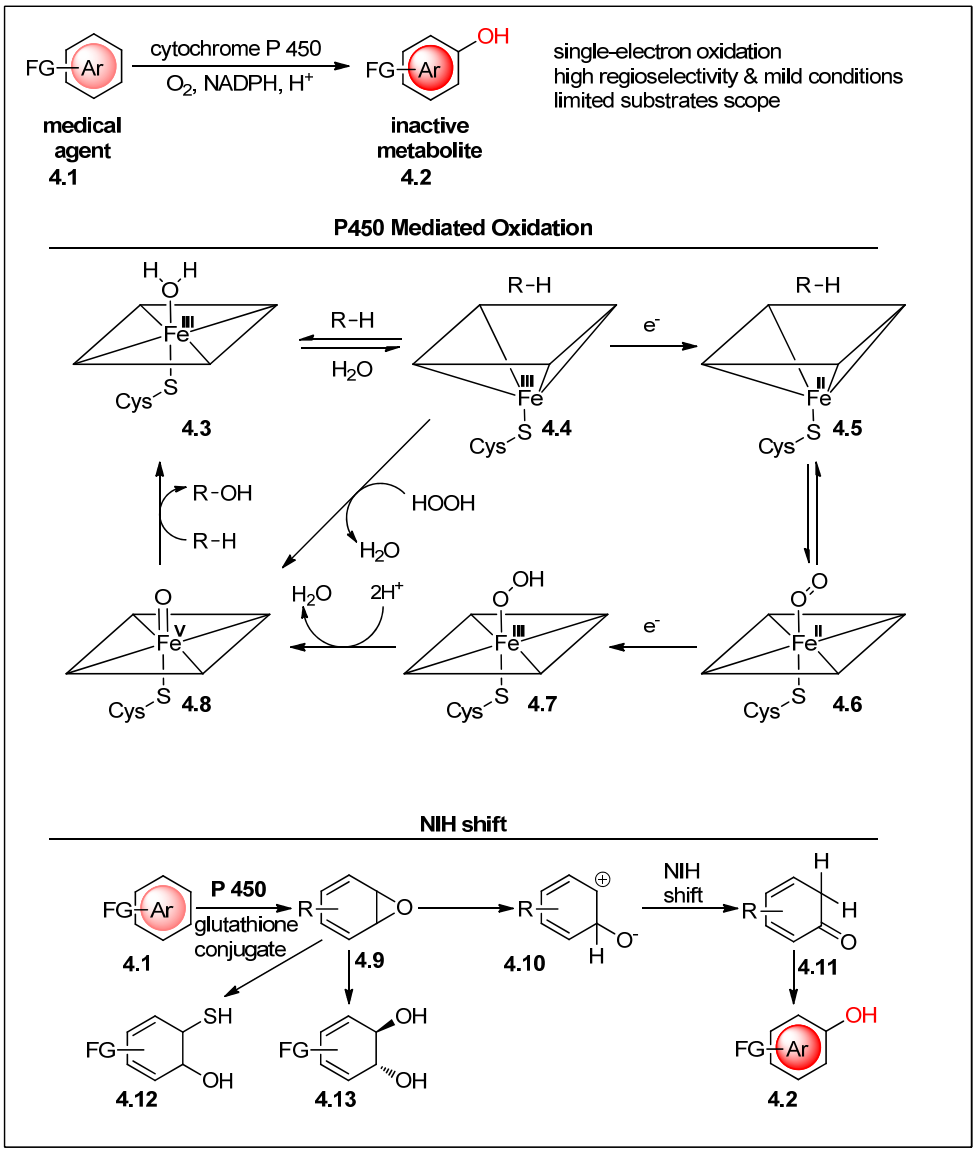
4.1 Introduction

Since the discovery of phenol in 1834 by Runge from coal tar advances have been made in synthesizing substituted phenols which are fundamental components in industrial, pharmaceutical, and natural occurring compounds.[1] Historically, the methods for the synthesis of phenols focused on Lewis acid assisted electrophilic aromatic substitutions, radical reactions and metal mediated C–H functionalization to directly hydroxylate the arene of interest.[2] However, direct hydroxylation of arenes without pre-functionalized precursors still remains a challenge. The methods using Lewis acids or Brønsted acid combined with excess oxidants are limited in their substate scope due to the strongly acidic and oxidizing nature of the reaction.[3] Transition metal catalyzed C–H oxidation of arenes with or without a directing group has been developed, and the reaction can be accomplished at both sp^2- and sp^3-C–H bonds.[4] We have found phthaloyl peroxide functions remarkably well converting arenes to phenols, as only the aromatic C–H bonds are oxidized in the presence of active C–H bonds, such as tertiary and benzylic C–H bonds. In addition the reaction has a high degree of tolerance for a wide array of functional groups. This mild, metal-free, and operationally simple method for the aryl-specific hydroxylation is also suitable for transformations of complex natural products and late-stage synthetic intermediates. In addition to synthetic studies, density functional theory (DFT) calculations show that this new reaction proceeds through a diradical mechanism identifying the origins of the exclusive selectivity for aromatic C–H bonds.

4.2 Background of Phenolic Compound Synthesis

In nature, oxidase P450 oxidizes a variety of small molecules to enhance their excretion and clearance. This included the conversion of arenes **4.1** to hydroxyl containing compounds including phenols **4.2**.[5] The reaction of alkanes proceeds through a oxidative process dubbed the rebound mechanism (Scheme 4.1). The oxidation processed through Fe (III) coordinated to porphyrin and cysteine. In the oxidation sequence, **4.4** is reduced to **4.5** which facilitates oxygen approaching to form intermediate **4.6**. As the iron-oxygen complex **4.6** is further reduced to **4.7**, the intermediate will be oxidized to **4.8** with an Fe (V) core. As the substrate is positioned within the enzyme it will oxidize it to form **4.3** for the next catalytic cycle in a related process. The oxidation of arenes to phenols by P450 enzyme proceeds through the NIH shift, generating the phenolic products **4.2** from arenes **4.1** through a 1,2-hydride shift mechanism of the epoxide precursor **4.09**.[6]

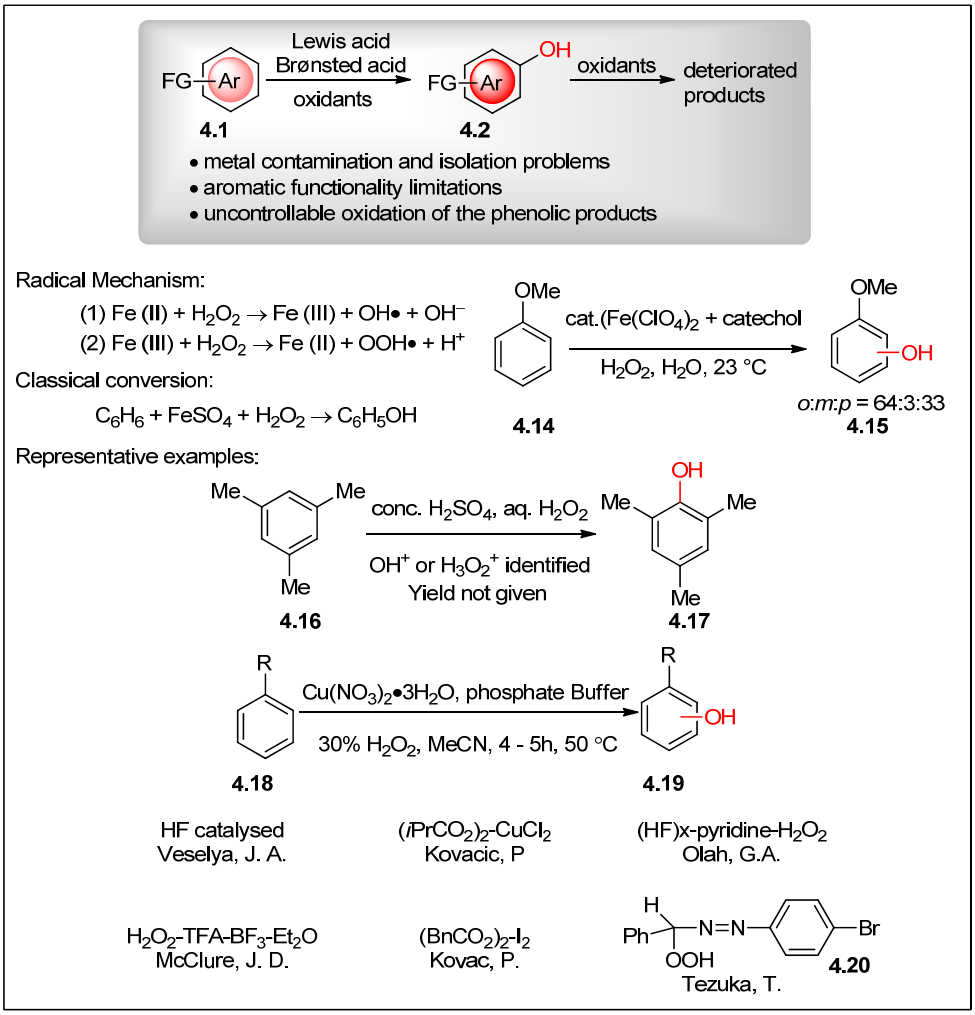
Scheme 4.1. P450 hydroxylation of arenes.



An overview of synthetic approaches for the direct synthesis of phenols is shown in Scheme 4.2. In almost all of the examples the oxidant is the limiting reagent, limiting the utility of this approach when the substrate is valuable. The reason for this less than ideal stoichiometery is that the products of the reactions, phenols, are more reactive than the starting arenes to the reaction conditions. Fenton's reagent has been studied for the hydroxylation of arenes, however,

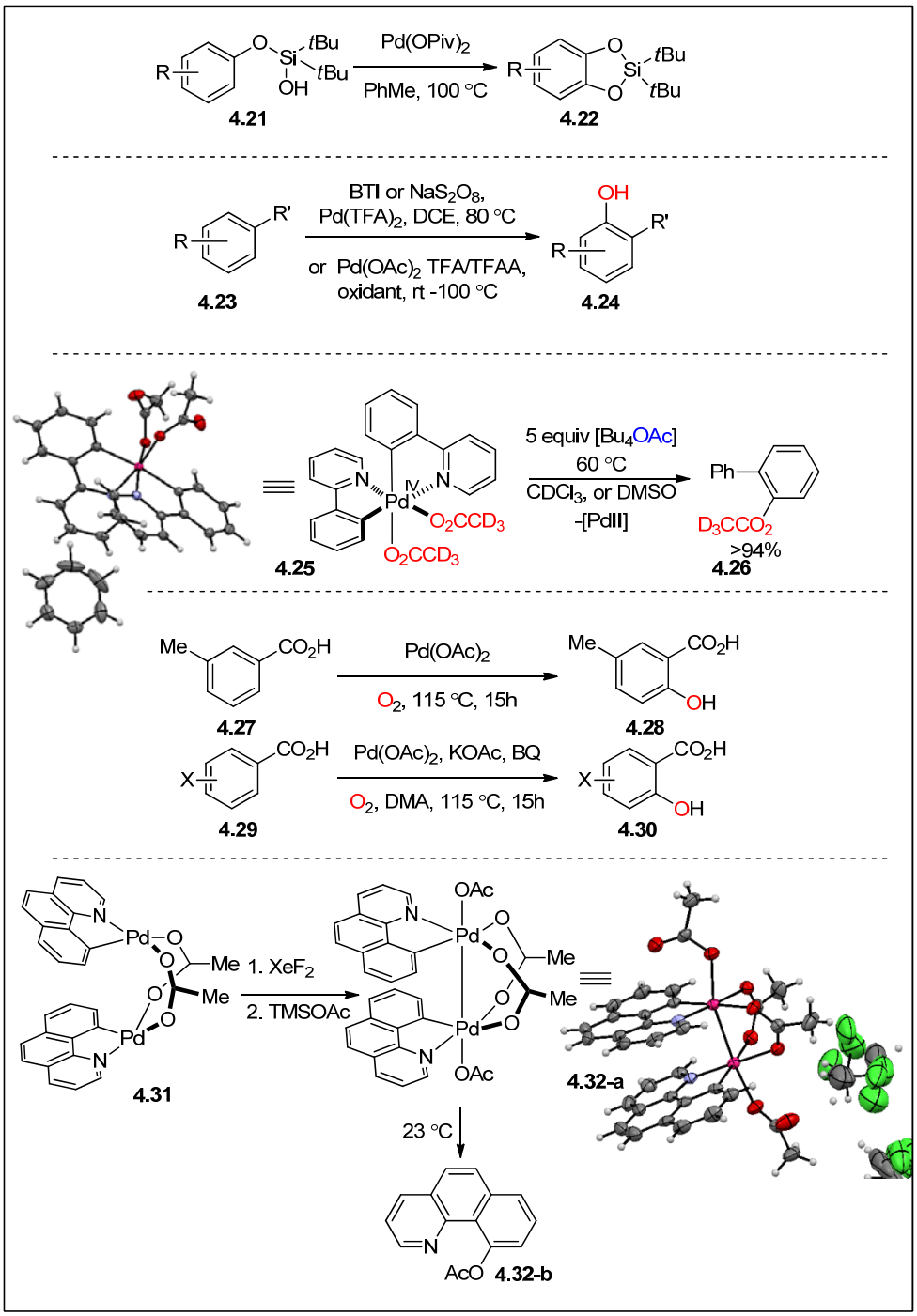
its primary use, waste water purification highlights the challenges using this reagent, namely it is an indiscriminate oxidant.[7, 8] In addition to problems of over oxidation there are severe limitations on the functional group compatibility using these methods.

Scheme 4.2. Lewis acid mediated hydroxylation of arenes.



Transition metal-catalyzed hydroxylation of arenes have been developed (Scheme 4.3). Notable achievements have been accomplished by Crabtree,[2e] Sanford,[4f, g] Yu,[4h] Ritter,[4k] Gevorgyan,[4i, j] Dong,[9] and Rao[10].[2d] In general the hydroxylation reactions use directing groups and the hydroxylation occurs at the expected position in good to excellent yields.

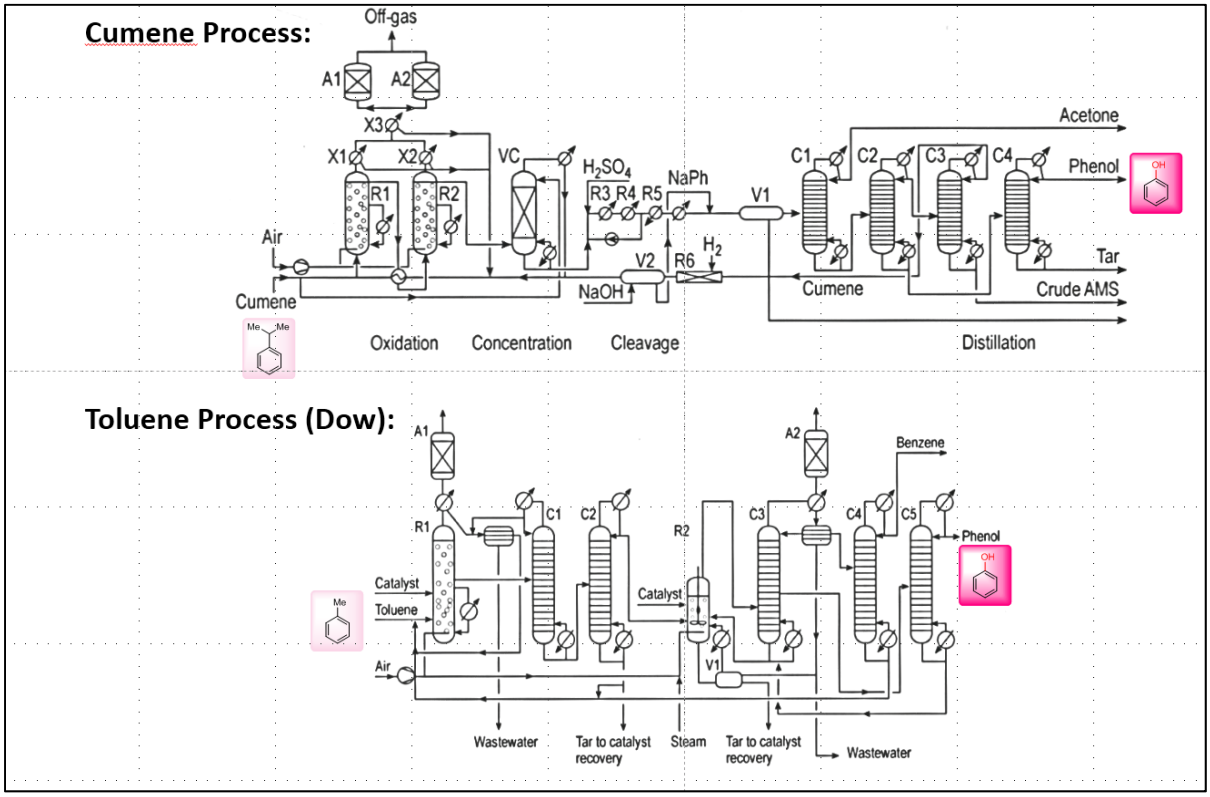
Scheme 4.3. Transitional metal-catalyzed hydroxylation of arenes.



In industry phenol is prepared through two major processes the cumene process and the toluene process (Scheme 4.4).[11] In the first flow chart of the cumene oxidation process there are

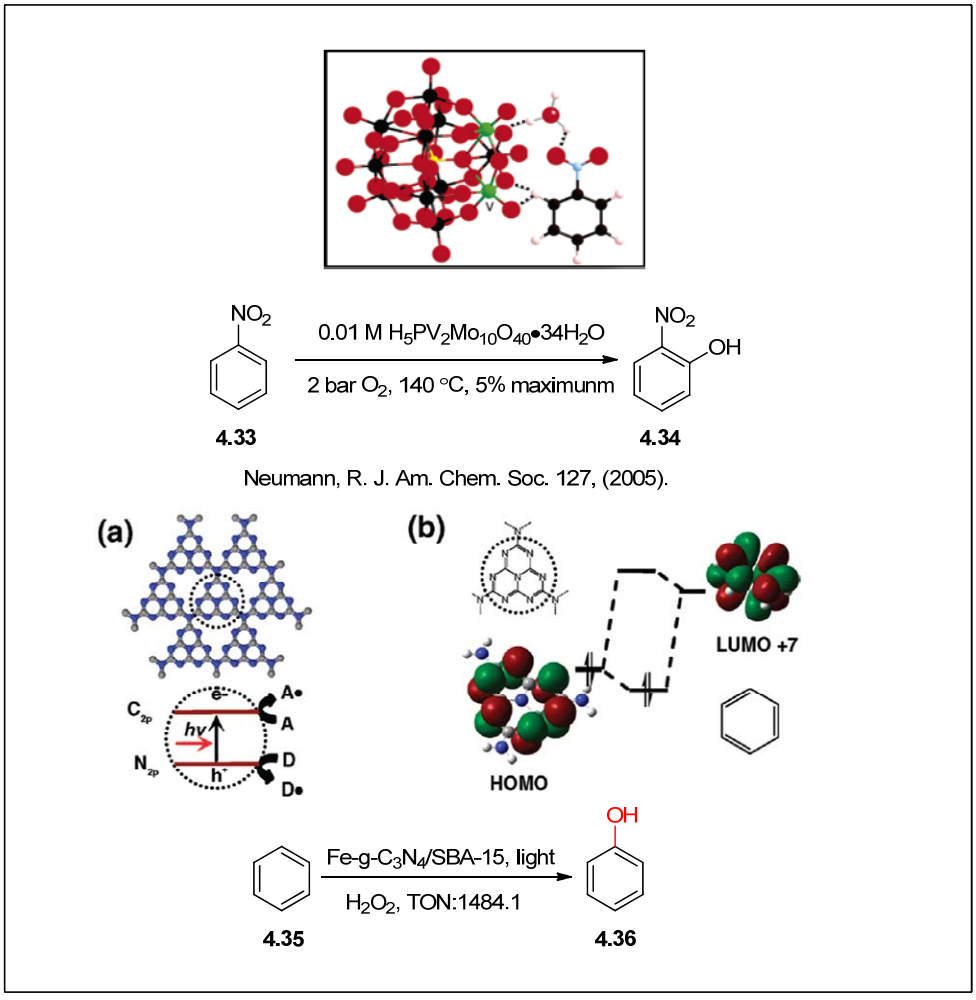
four major steps including oxidation, concentration, cleavage and distillation. In Dow's improved process, toluene is used as the feedstock to reduce cost.

Scheme 4.4. Cumene and toluene oxidation processes.



Additional oxidative approaches have been developed as shown in Scheme 4.5 where a Mo complex was used to hydroxylate nitrobenzene **4.33** under heterogeneous condition to give the desired product **4.34**.[12] Wang and coworkers were able to hydroxylate benzene using light and oxygen as well.[13]

Scheme 4.5. Additional methods for the synthesis of phenols.



4.3 Hydroxylation of Arenes to Phenols Using Phthaloyl Peroxide

Following from our studies centered on the dihydroxylation of alkenes the reactions of arenes[14] with phthaloyl peroxide was examined. The initial substates for the reaction were mesitylene and 1,3,5-triisopropyl benzene. Initial success was achieved using dichloroethane as a solvent, providing the phthaloylated adduct **4.37** in 35% yield (Figure 4.1).

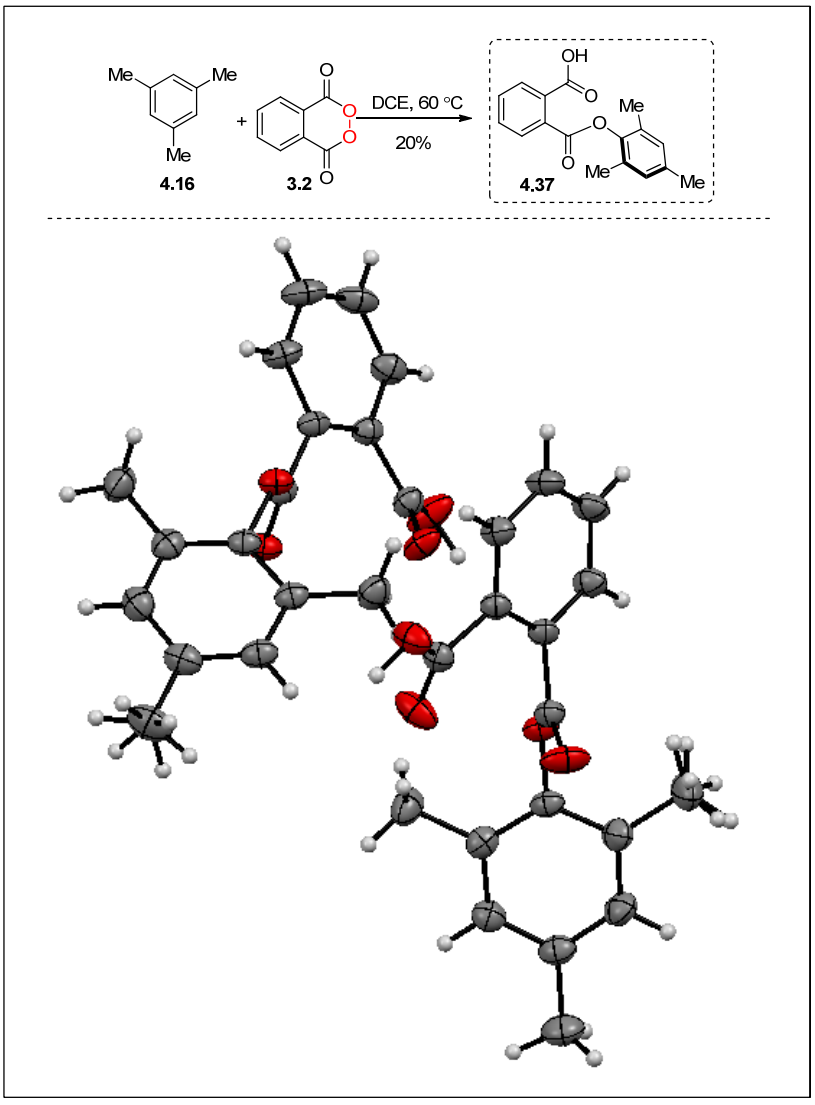
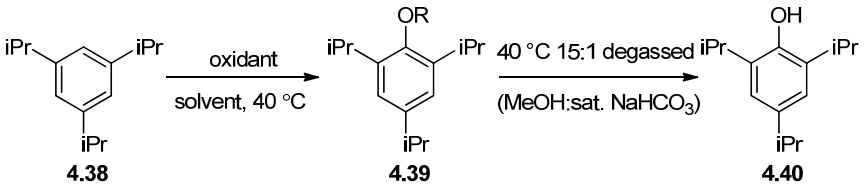


Figure 4.1. Crystal structure of compound **4.37**.

Subsequently solvents were systematically investigated to provide optimal conditions for the hydroxylation of **4.38**. While standard solvents gave low yields of **4.40**. Fluorinated solvent including trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) at ambient temperatures increased the yield to 97%. The cyclic malonyl peroxide **4.41** was similarly effective (93% yield)

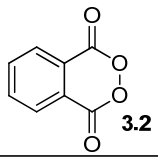
Table 4.1. Optimization of the hydroxylation of **4.18** by phthaloyl peroxide **3.2**.



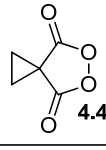
4.38 **4.39** **4.40**

Entry	oxidant/equiv.	solvent	yield
1	**3.2**/ 2 equiv.	**DCE**	**32%**
2	**3.2**/ 2 equiv.	**DCM**	**30%**
3	**3.2**/ 2 equiv.	**EtOAc**	**< 5%**
4	**3.2**/ 2 equiv.	**DMSO**	**0**
5	**3.2**/ 2 equiv.	**1,4-dioxane**	**< 5%**
6	**3.2**/ 2 equiv.	**DMF**	**0**
7	**3.2**/ 2 equiv.	**DME**	**0**
8	**3.2**/ 2 equiv.	**benzene**	**< 5%**
9	**3.2**/ 2 equiv.	**toluene**	**< 5%**
10	**3.2**/ 2 equiv.	**MeCN**	**mixtures**
11	**3.2**/ 2 equiv.	**C_6F_{14}**	**0**
12	**3.2**/ 2 equiv.	**per-F-tBuOH**	**70 - 90%**
13	**3.2**/ 2 equiv.	**TFE**	**85%**
14	**3.2**/ 2 equiv.	**HFIP**	**97%**
15	**4.24**/ 2 equiv.	**HFIP**	**93%**
16	**4.25**/ 10 equiv.	**HFIP**	**0**
17	**4.26**/ 10 equiv.	**HFIP**	**0**
18	**4.27**/ 1.1 equiv.	**HFIP**	**0**
19	**3.2**/ 1.2 equiv.	**HFIP**	**90%**
20	**3.2**/ 1.3 equiv.	**HFIP**	**97%**
21	**3.2**/ 1.3 equiv.	**HFIP**	**sluggish**
22	**3.2**/1.5 equiv.	**HFIP**	**< 10%**
23	**3.2**/1.5 equiv.	**HFIP**	**< 10%**

Oxidants:



3.2



4.41

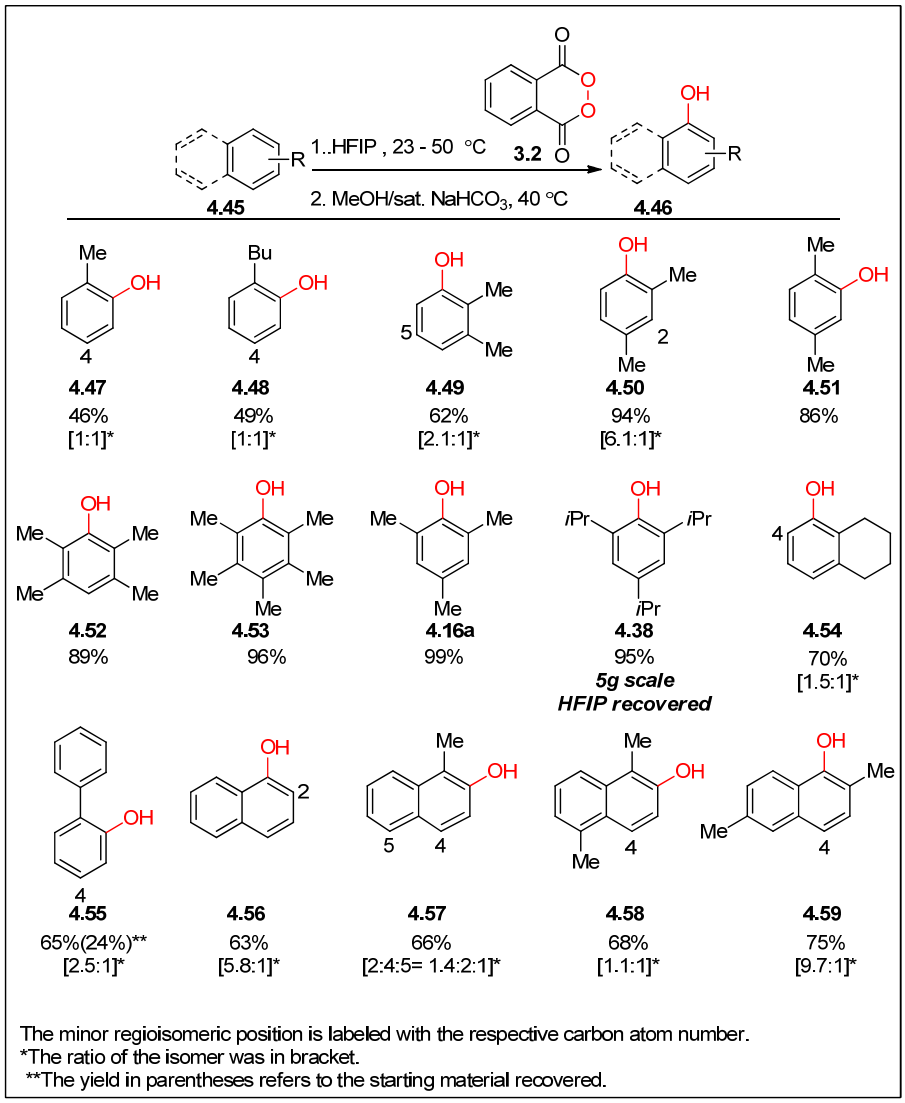
10% tBuOOH **4.42**

30% H_2O_2 **4.43**

BPO **4.44**

The new protocol allowed the direct incorporation of hydroxyl groups into a broad range of arenes as summarized in Table 4.2. Toluene **4.47** was hydroxylated to give a 1:1 ratio of o-cresol and p-cresol in 46% yield. Interestingly we did not observe any over oxidized product. Compounds **4.48-4.53** reacted well providing the corresponding phenols in 49-99% yield. Oxidation of polycyclic aromatic hydrocarbons generated the expected phenolic products **4.54-4.59** in yields of 63-75%.

Table 4.2. Hydroxylation of aliphatic substituted arenes **4.45** by phthaloyl peroxide **3.2**.



We studied the decomposition of phthaloyl peroxide by thermogravimetric analysis (Figure 4.2). The therogravimetric data for **3.2** is shown as the red line showed that below 100 ºC peroxide **3.2** is stable however above 110 ºC the solid decomposed rapidly. In comparison, the peroxide **4.41** was also subjected to TGA (black line). This peroxide was less thermally stable but had a gradual decomposition.

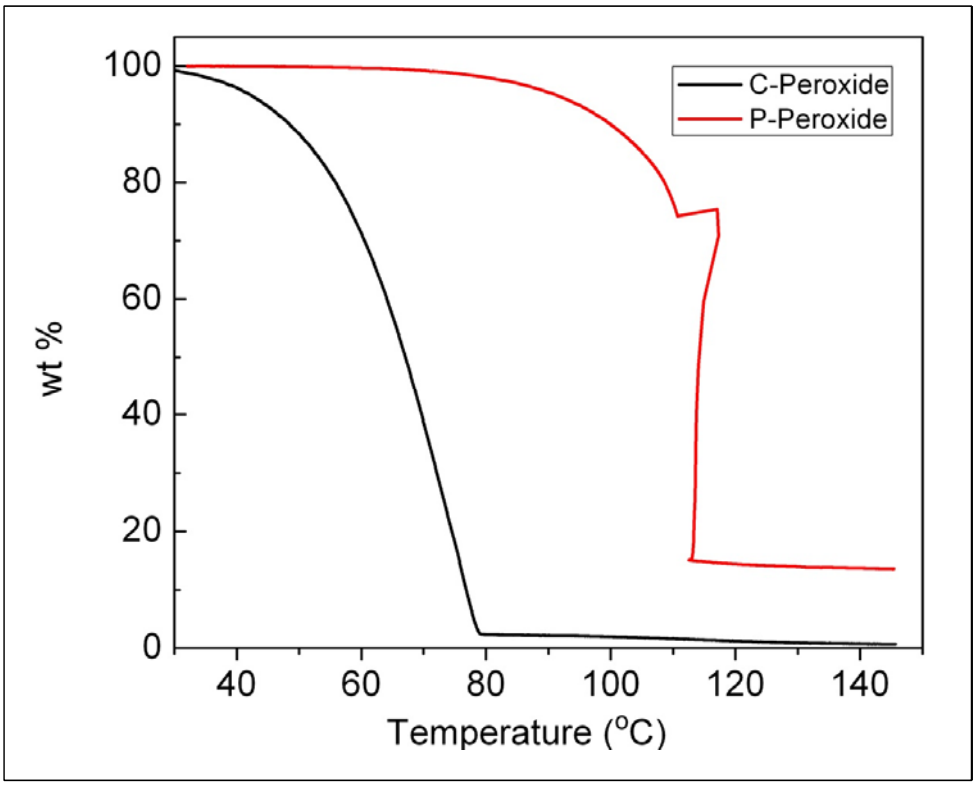
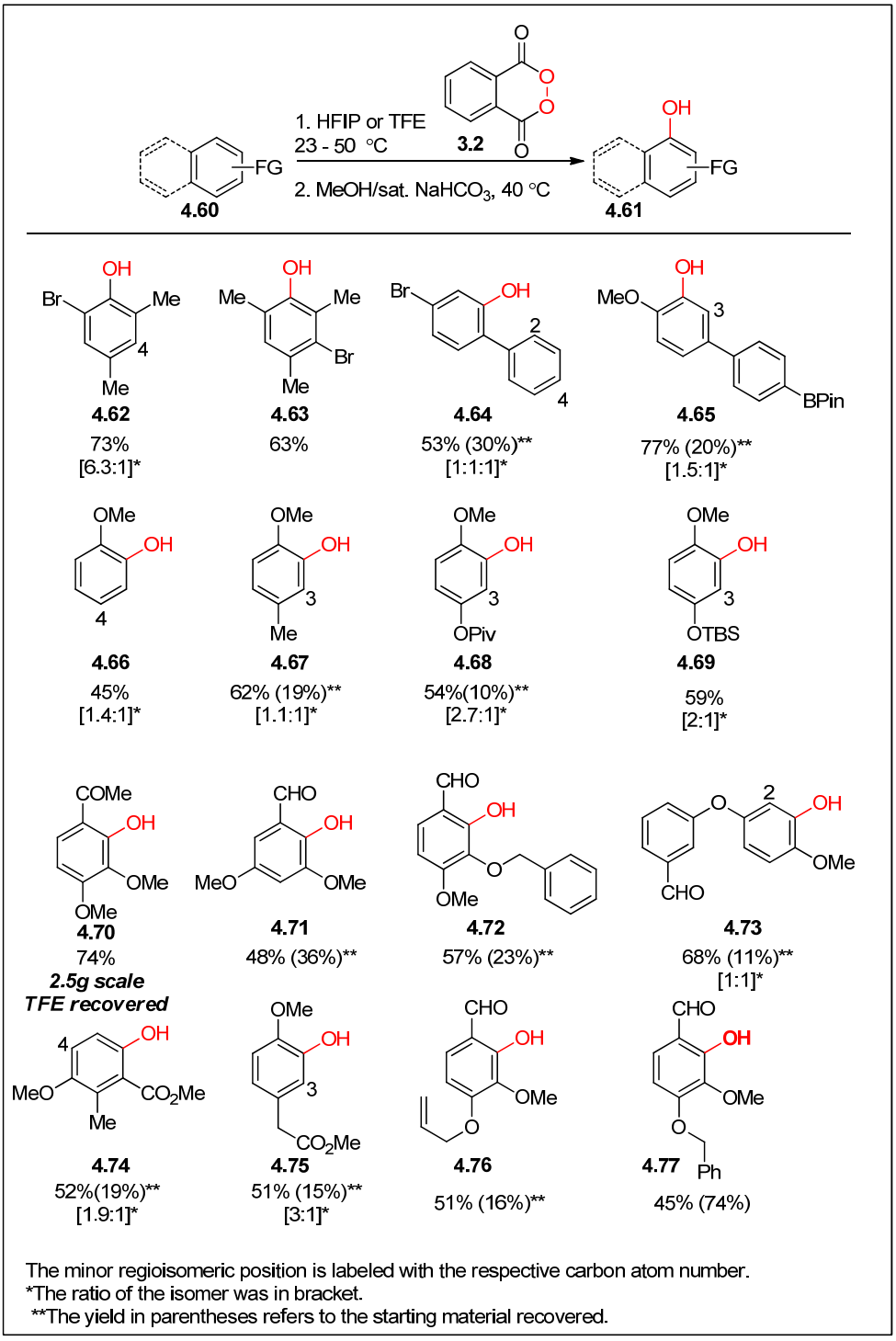


Figure 4.2. TGA data of peroxides **3.2** and **4.41**.

The oxidation of functionalized arenes is presented in Table 4.2. Aryl halides **4.62** and **4.63** showed good reactivity providing the desired products in 73% and 63% yield respectively. Oxidation of bromide **4.64** or boronate **4.65** showed selectivity favoring hydroxylation on phenyl

ring without effecting bromine or boron. Oxidations of anisole and its derivatives also gave corresponding products **4.66**-**4.69** in medium yield (45-62%). Aldehydes and ketones underwent oxidation with no evidence of Bayer-Villager oxidation with the products **4.70** or **4.71** formed in good yields.[15] Even alkenes were inert under the reaction conditions as **4.76** was generated in 51% yield with 16% recovered starting material.

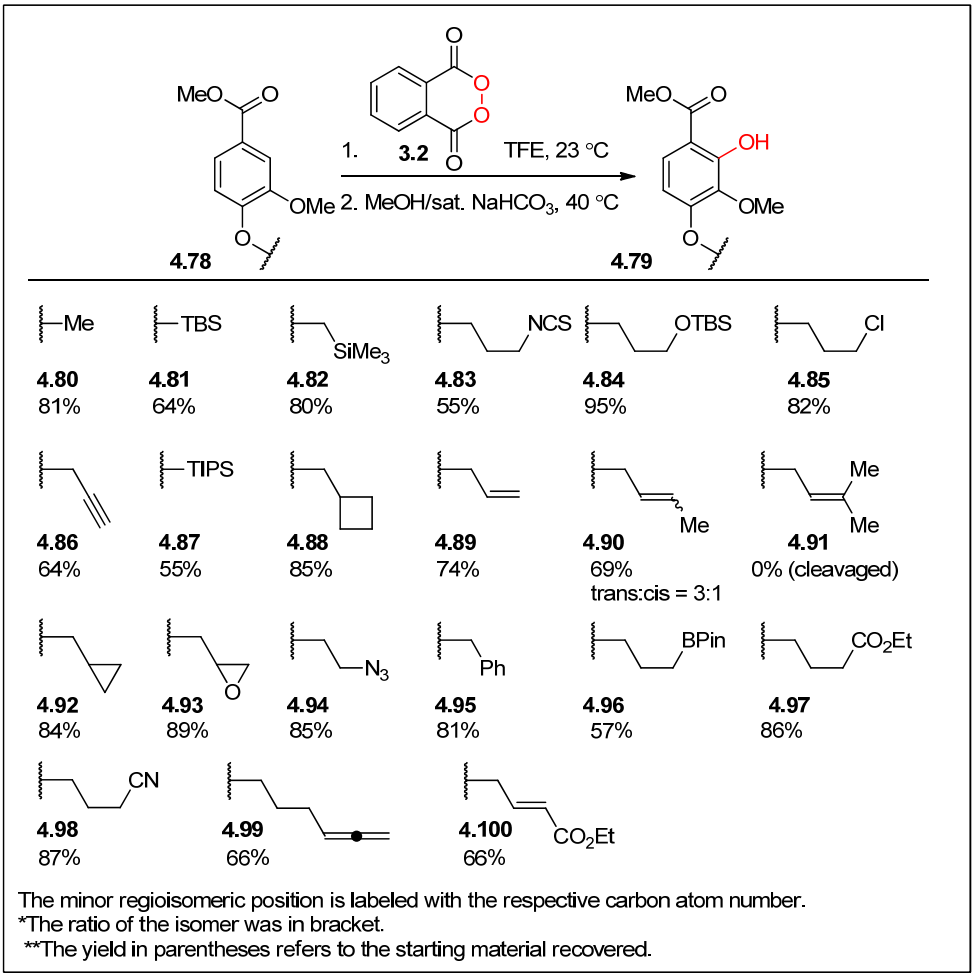
Table 4.3. Hydroxylation of functionalized arenes by phthaloyl peroxide **3.2**.



The minor regioisomeric position is labeled with the respective carbon atom number.
*The ratio of the isomer was in bracket.
**The yield in parentheses refers to the starting material recovered.

A series of functionalized vanillate derivatives **4.80**-**4.90** were successfully synthesized to showcase the functional group compatibility of peroxide **3.2** (Table 4.4). Alkyl silane **4.82**, azide **4.94**, pinacol boronate **4.96** and allene **4.99**, were all tolerated under the reaction conditions.

Table 4.4. Hydroxylation of vanillate derivatives by phthaloyl peroxide **3.2**.

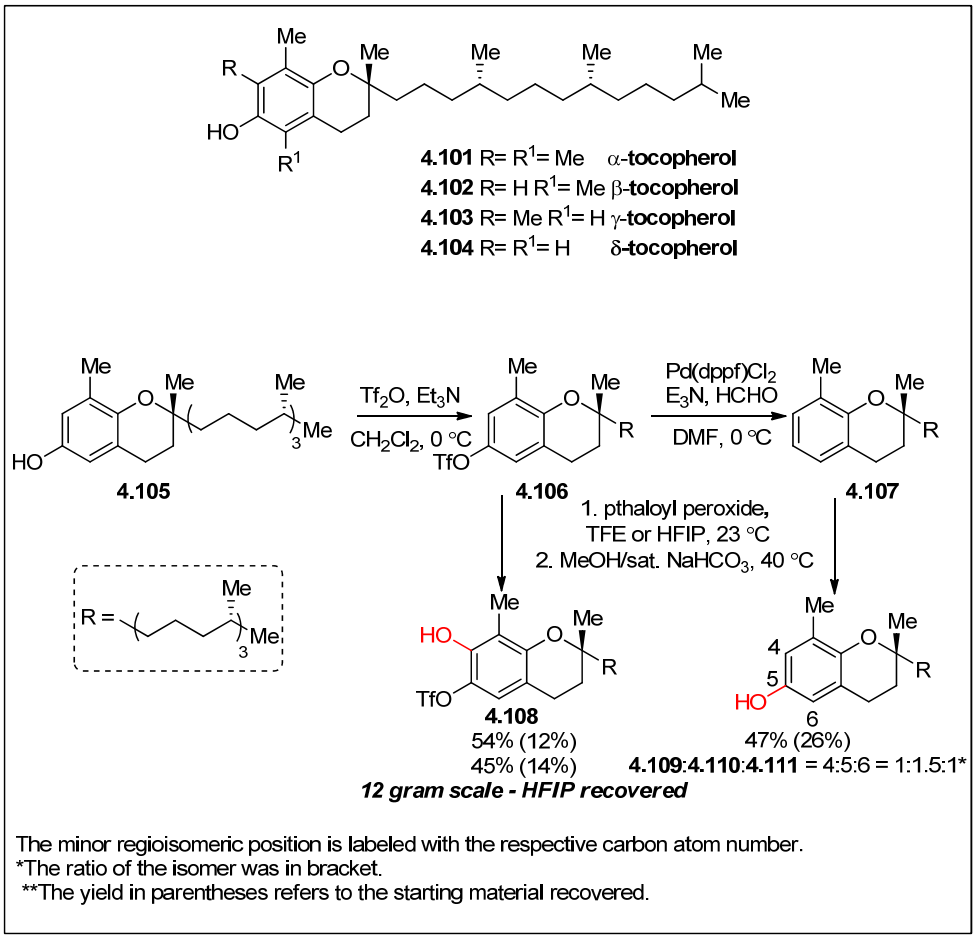


The minor regioisomeric position is labeled with the respective carbon atom number.
*The ratio of the isomer was in bracket.
**The yield in parentheses refers to the starting material recovered.

Based on the compatibility of functional groups late stage oxidative modification a number of complex molecules was investigated. The natural product (+)-γ-tocopherol **4.104** was selected based on its biological activity acting as a chemopreventative agent (Scheme 4.6).[16] Reaction of dehydroxy-(+)-γ-tocopherol **4.107** with peroxide **3.2** formed **4.109**, **4.110**, and **4.111** in 47% combined yield and returned 23% of the starting material. Reaction of triflate **4.106**

under the same condition generated **4.108** as the sole produced in 54% yield along with 12% of **4.106** recovered.

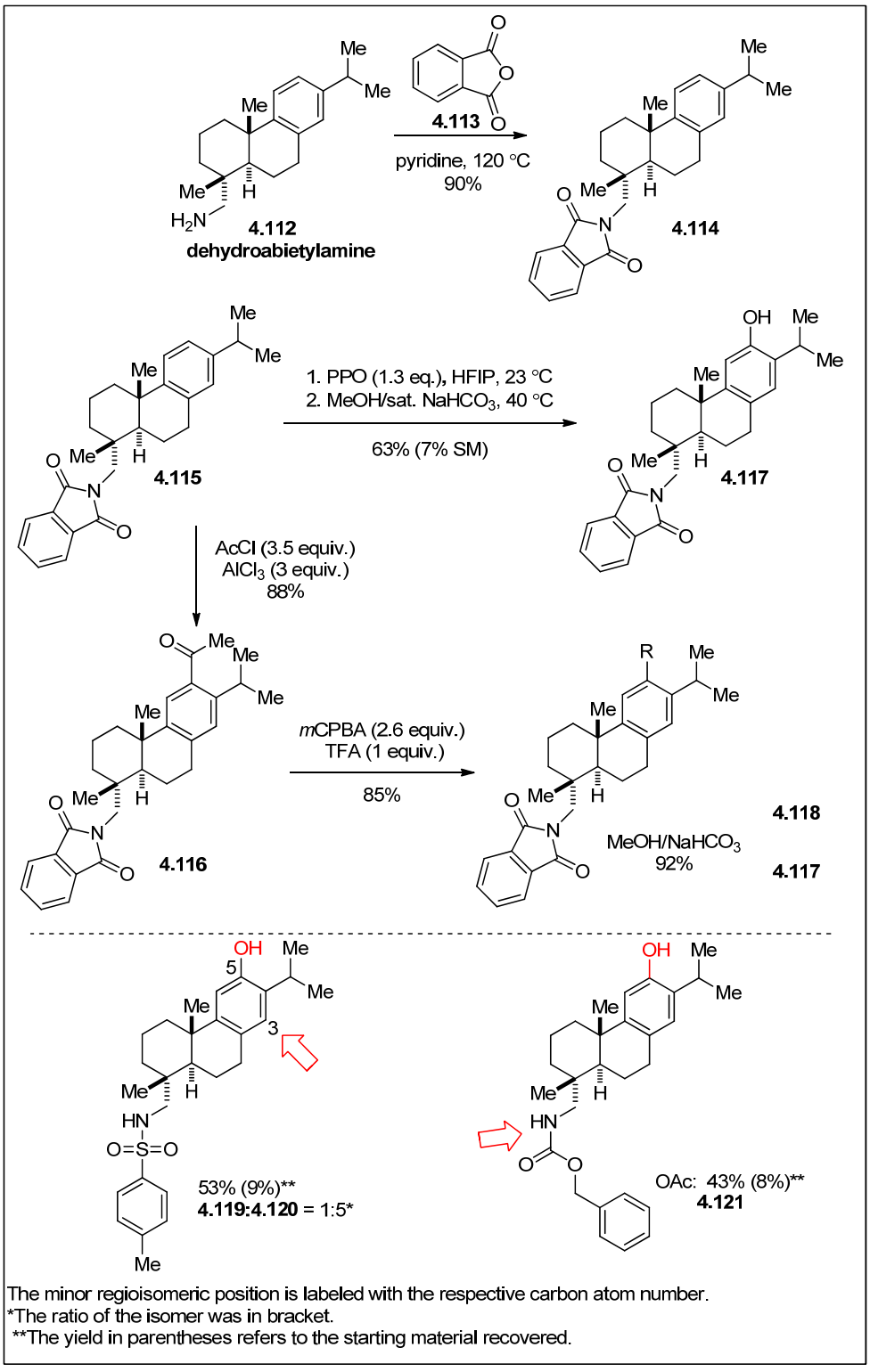
Scheme 4.6. Phthaloyl peroxide **3.2** mediated hydroxylation of tocopherol derivatives.



Hydroxylation of dehydroabietylamine derivatives is shown in Scheme 4.7. Dehydroabietylamine **4.112** and its derivatives possess antiinflammatory activities.[17] The dehydroabietylamine phenolic derivatives **4.117** was previously synthesized in a three step sequences in 69% yield using standard Friedel Crafts/Bayer-Villager chemistry. In comparison, substrate **4.115** was reacted under our standard conditions to form phenol **4.117** in 57% yield. Comparing the to the original reported protocol,[18] the phthaloyl peroxide oxidation avoided the

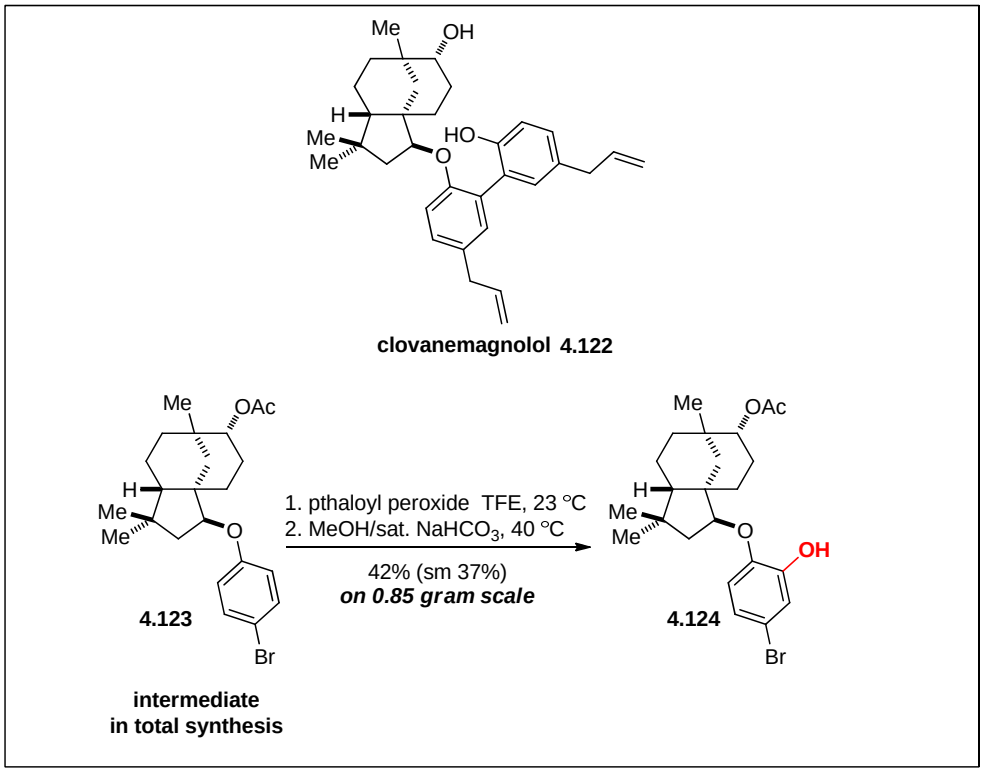
use of excess aluminum reagents and oxidants. The step economy[19] was dramatically improved. The sulfonyl dehydroabietylamine derivative **4.112** gave products **4.119** and **4.120** in 53% yield. The Cbz dehydroabietylamine phenol **4.121** was also prepared in similar yield.

Scheme 4.7. Phthaloyl peroxide **3.2** mediated hydroxylation of dehydroabietylamine derivatives.



Clovanemagnolol **4.122**, isolated from the bark of the bigleaf Magnolina tree, was shown to have neuronal growth promoting effects (Scheme 4.8).[20] Followed the literature synthesis 850 mg of precursor **4.124** was prepared and subjected to the phthaloyl peroxide **3.2** mediated oxidation and the the hydroxylated product **4.124** was isolated in 42% yield with 37% recovered starting material.

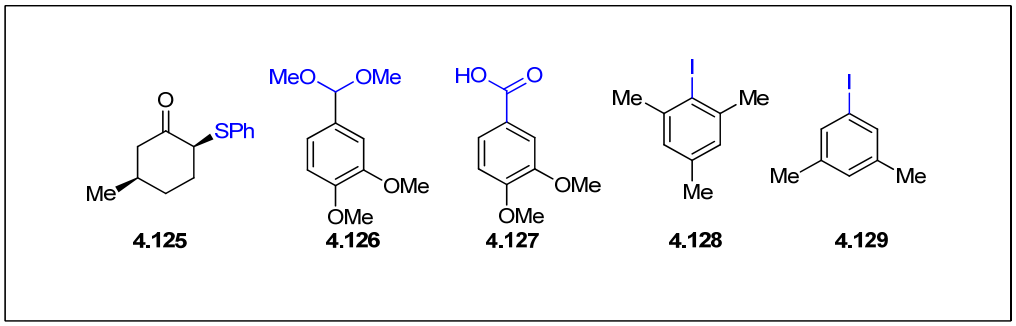
Scheme 4.8. Phthaloyl peroxide **3.2** mediated hydroxylation clovanemagnolol derivative **4.123**.



While the reaction worked with a variety of functionality the reaction failed with the substartes shown in Scheme 4.9. We found that thioether **4.125** was oxidized at sulfur. The acetal **4.126** was hydrolyzed under the acidic reaction condition. Acid **4.127** has significant purification problem. It should also be noted that the iodobenzenes similar to **4.128** or **4.129** are not substrates as there is likely oxidation at iodine providing iodoso compounds. Only the electron

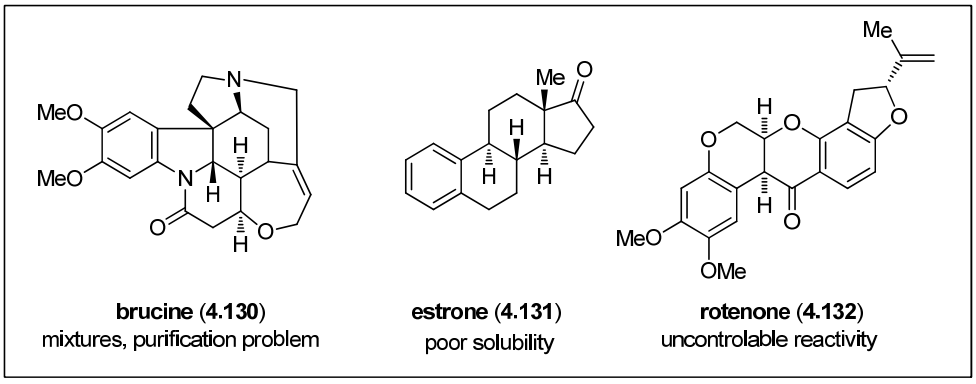
rich or neutral aromatic compounds were found to be suitable substrates under these reaction conditions. Very electron rich compounds such as natural products brucine **4.130** or rotenone **4.132** provided none of the desired products possibly due to rapid oxidation of the resulting phenolic compounds, more a limitation of the compounds themselves. Solubility under the reaction conditions was also important as the estrone **4.131**, insoluble in the fluorinated alcoholic solvent, was recovered from the reaction unchanged (Scheme 4.10).

Scheme 4.9. Incompatible functional groups for the phthaloyl peroxide-mediated hydroxylation.



4.125 **4.126** **4.127** **4.128** **4.129**

Scheme 4.10. Unsuccessful hydroxylation at selected natural product derivatives.



brucine (**4.130**)
mixtures, purification problem

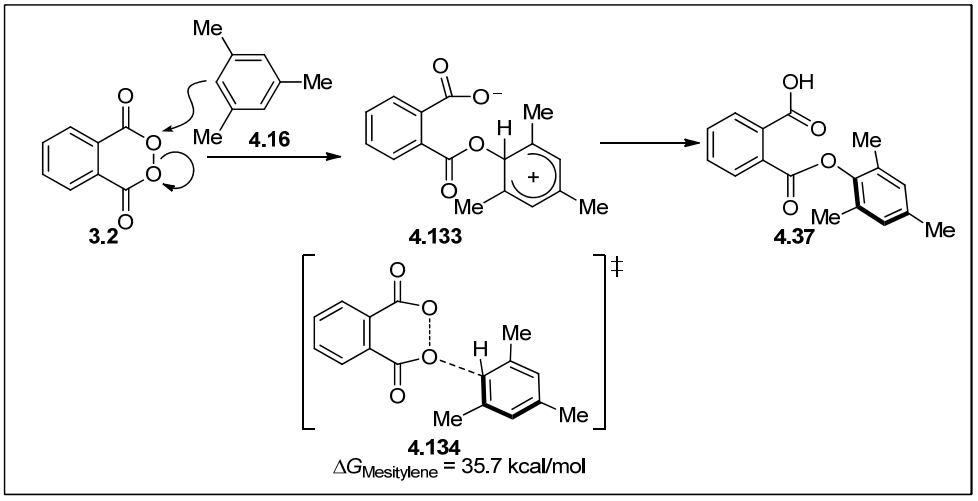
estrone (**4.131**)
poor solubility

rotenone (**4.132**)
uncontrolable reactivity

4.4 Mechanistic Study of the Hydroxylation of Reaction

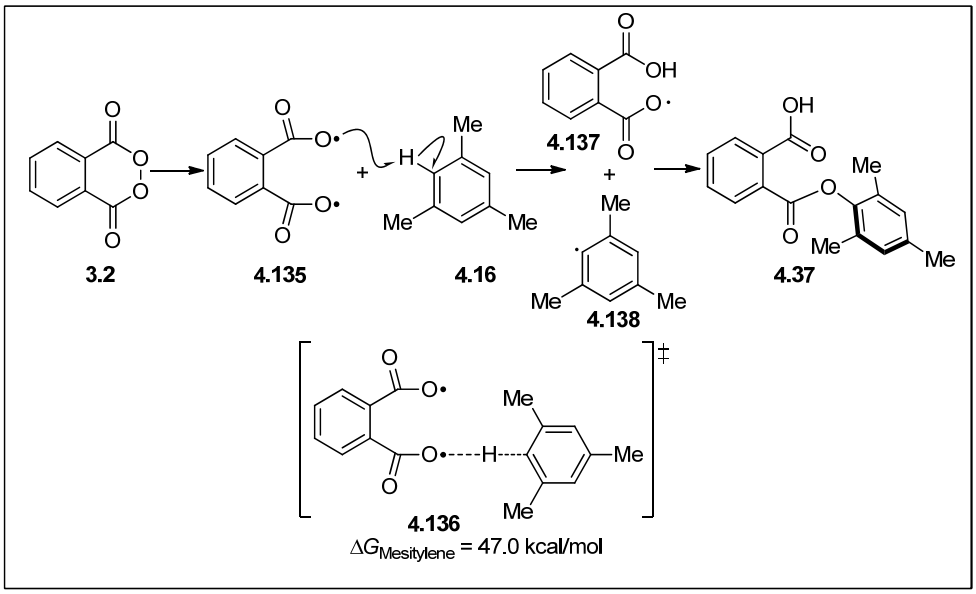
It is great honor to collaborate with Yong Liang and K. N. Houk in UCLA, we were able to evaluate the reaction mechanism through three different processes. The first process was the direct attack of mesitylene **4.16** onto the peroxide through the transition state **4.134**. The transitional state for **4.134** showed an energy of 35.7 kcal/mol (Scheme 4.11).

Scheme 4.11. DFT for an ionic mechanism.

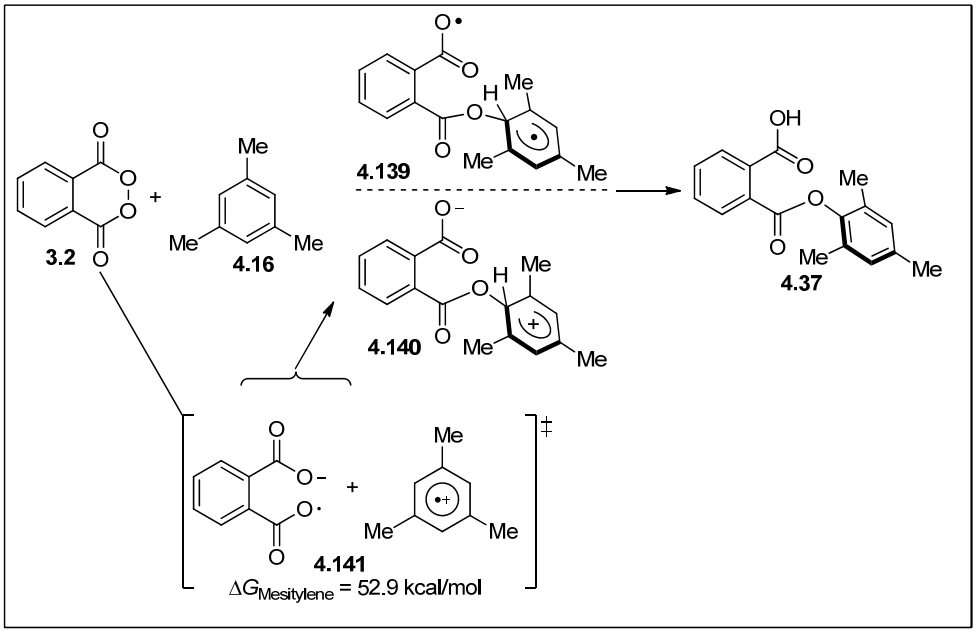


In Scheme 4.12 the energy for the direct abstraction of a hydrogen from mesitylene was found to be 47.0 kcal/mol, a significant barrier. Being even higher (Scheme 4.13) the mechanism going through a single electron transfer was ruled out as **4.141** was computed to lead to an energy barrier of 52.9 kcal/mol.

Scheme 4.12. DFT analysis of Csp^2-H activation mechanism.

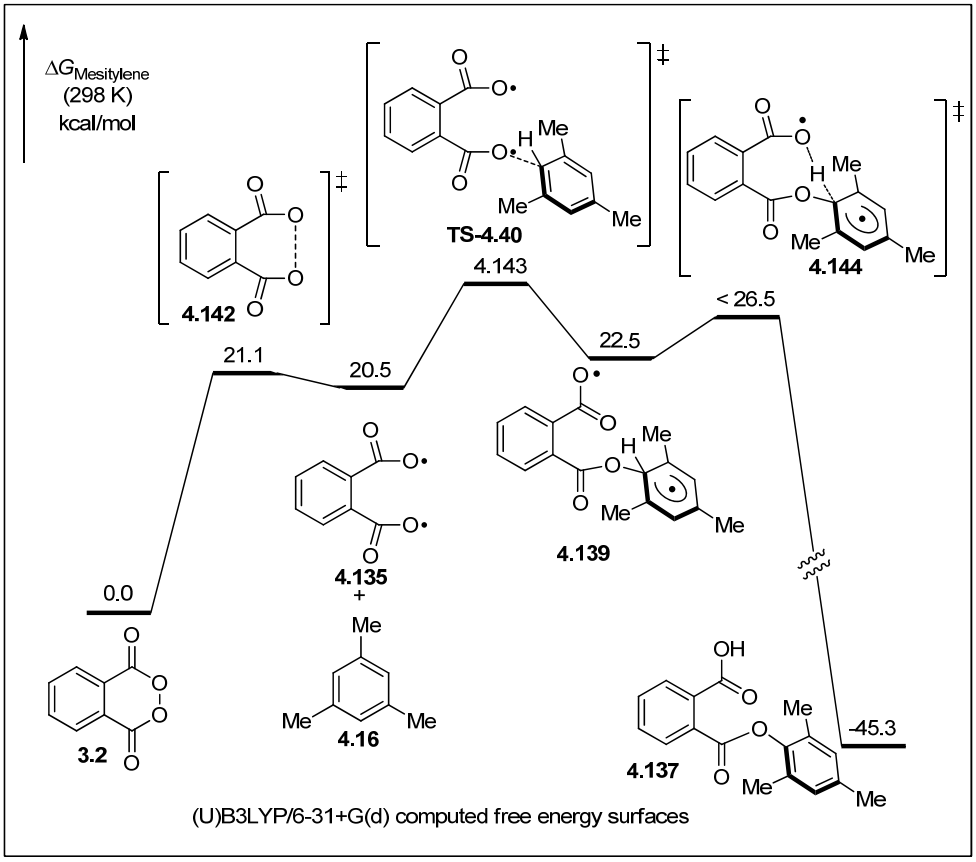


Scheme 4.13. DFT analysis of SET mechanism.



On the basis of quantum mechanical calculations, this metal-free aromatic C–H oxidation most likely occurs through a reverse rebound diradical mechanism (Scheme 4.14). Multiple computational tests using density functional theory (DFT) and ab initio methods were investigated. The energy required from diradical **4.135** was found to be 8.6 kal/mol with a 21.1 kcal/mol barrier for the homolysis of the peroxide bond.

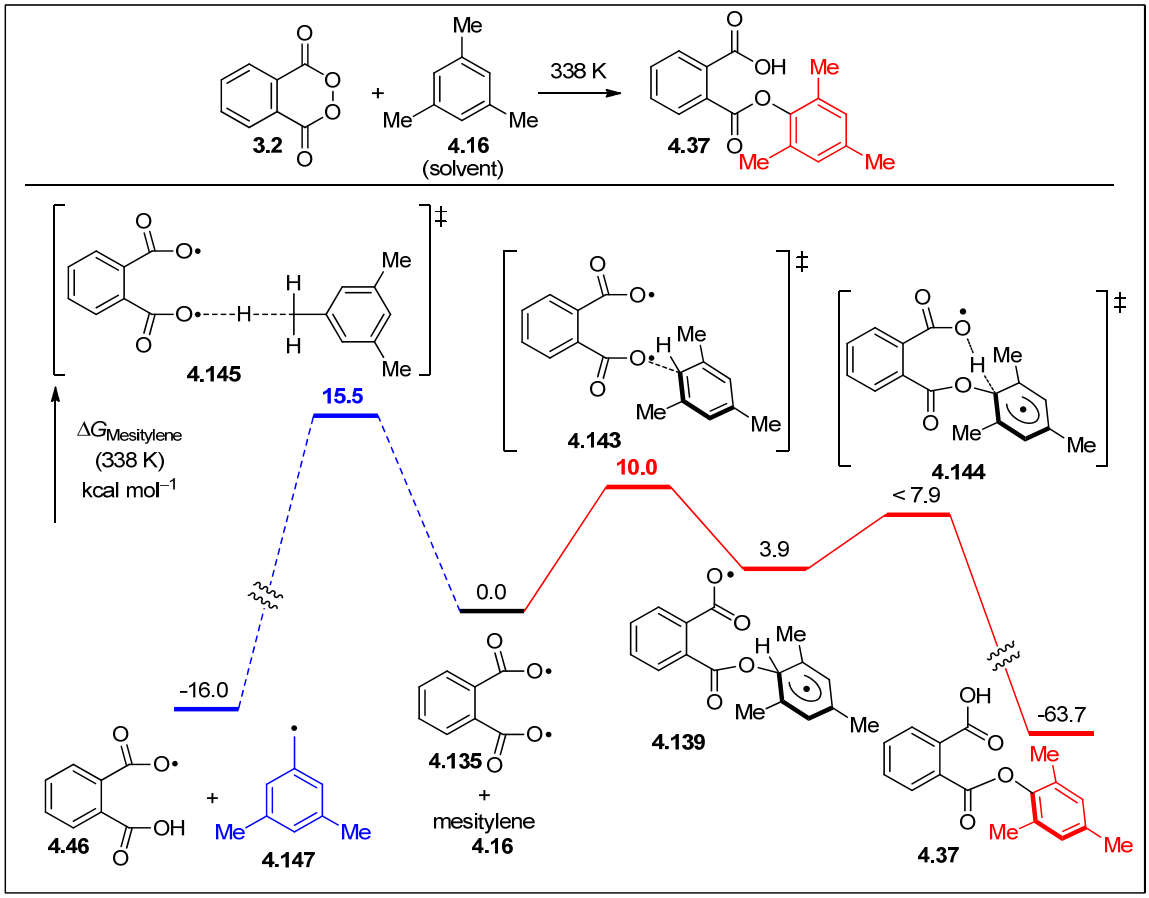
Scheme 4.14. DFT analysis of the reversed rebounded mechanism.



The reaction's selectivity for aryl C-H bonds relative to benzlic C-H bonds was also investigated. The free energy surfaces for reactions of the aromatic and benzylic C–H bonds of mesitylene **4.16** with diradical **4.135** from phthaloyl peroxide **3.2** or benzoyloxy radical **4.150** are shown in Scheme 4.15. As illustrated, the addition of one radical center in **4.135** to the

aromatic ring of mesitylene requires a free energy of only 10.0 kcal mol^{-1}. The subsequent intramolecular hydrogen transfer is very facile with a barrier of less than 4 kcal mol^{-1}.

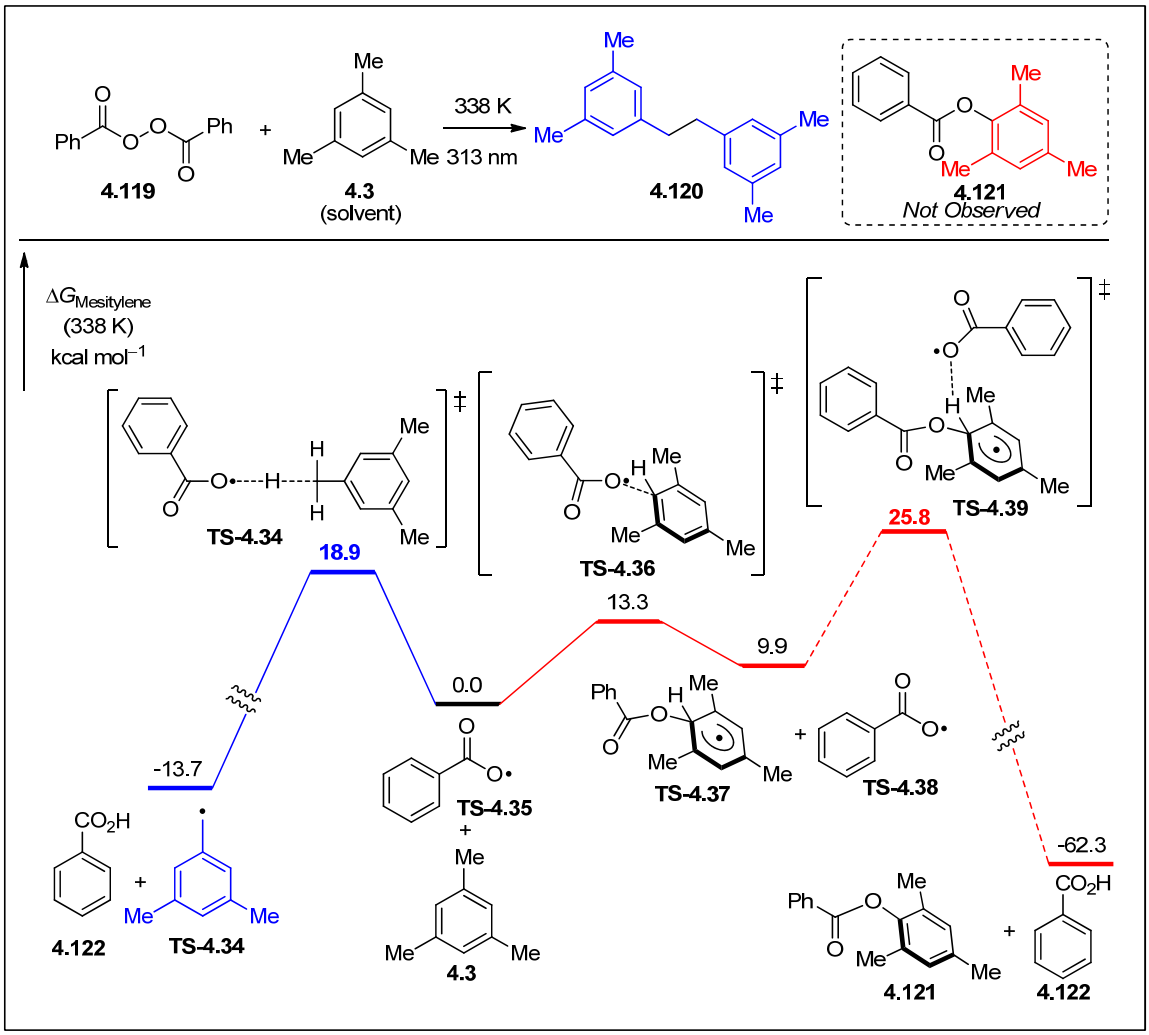
Scheme 4.15. Experimental results and CPCM-(U)B3LYP/6-31+G(d) computed free energy surfaces for the functionalization of aromatic and benzylic C–H bonds of mesitylene, reaction pathways involving diradical A generated from the thermal decomposition of phthaloyl peroxide.



The direct hydrogen abstraction to form benzylic radical **4.151** is disfavored, 5.5 kcal mol^{-1} higher than for the aromatic C–H functionalization. This difference accounts for the exclusive aryl-selectivity under experimental conditions. By contrast, benzoyloxy radical **4.150**, formed from benzoyl peroxide, reacts with mesitylene **4.16** to give only the benzylic C–H functionalized product under similar conditions. The computed activation energy for the benzylic

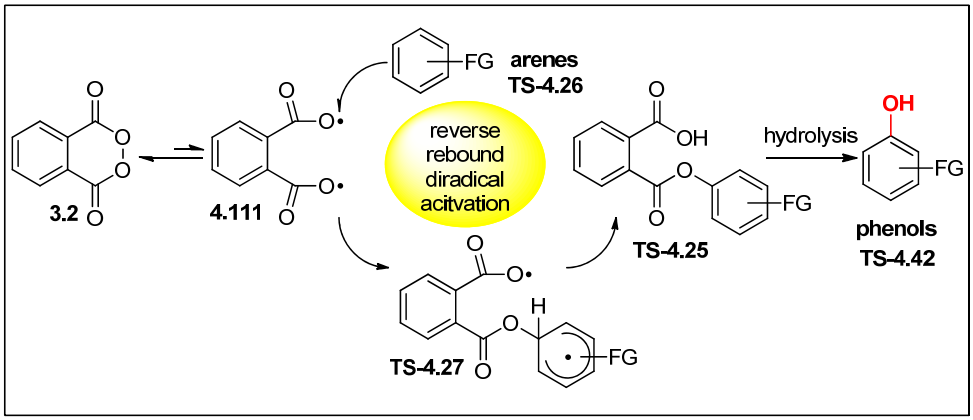
hydrogen abstraction by benzoyloxy radical (**4.150**) is 18.9 kcal mol^{-1}.[22] In this case, the two-step aromatic C–H functionalization is disfavored as the intermolecular hydrogen abstraction in **4.155** from radical intermediate **4.37** becomes rate-determining with a much higher overall barrier of 25.8 kcal mol^{-1}. This is in agreement with the experimental fact that benzoyloxy radical mediated aromatic C–H oxidation is not observed.

Scheme 4.16. Experimental results and CPCM-(U)B3LYP/6-31+G(d) computed free energy surfaces for the functionalization of aromatic and benzylic C–H bonds of mesitylene, reaction pathways involving benzoyloxy radical **4.150** generated from benzoyl peroxide under irradiation with 313 nm light.



At last, as summarized in Scheme 4.17, we successfully discovered, developed a useful method to hydroxylate arenes by phthaloyl peroxide **3.2** on a broad range of electron rich and neutral substrates.[22] What is more, we gained insights into the reverse rebound diradical mechanism for this transformation which would guide the application of this new mechanism in other research fields.

Scheme 4.17. Phthaloyl peroxide **3.2** mediated reverse rebound diradical activation.



4.5 Conclusion

In summary, the phthaloyl peroxide **3.2** mediated hydroxylation of arenes provides a new, selective method for the conversions of arenes to phenols. The hydroxylation procedure is performed under mild conditions without the utilization of metallic reagents or strong acids, saving time, cost, and purification steps. Moreover, this methodology possesses broad functional group compatibility, has excellent selectivity for aromatic C–H bonds, and does not lead to over-oxidation. The tolerance of the reaction toward a variety of functional groups permits the modification of advanced synthetic intermediates. Mechanistic insights into the reverse rebound process provides a novel strategy for selective C–H functionalization and lays the foundation for the discovery of new chemical transformations using diradical.

4.6 References

1. Rappoport, Z., *The chemistry of phenols*. Wiley-Interscience: 2003; Vol. 1.

2. (a) Olah, G. A.; Fung, A. P.; Keumi, T., Oxyfunctionalization of hydrocarbons. 11. Hydroxylation of benzene and alkylbenzenes with hydrogen peroxide in hydrogen fluoride/boron trifluoride. *Journal of Organic Chemistry* **1981,** *46* (21), 4305-4306; (b) Walling, C., Fenton's reagent revisited. *Accounts of Chemical Research* **1975,** *8* (4), 125-131; (c) Kurz, M. E.; Kovacic, P., Oxygenation of toluene with diisopropyl peroxydicarbonate-metal salt. Variation in the salt component. *The Journal of Organic Chemistry* **1968,** *33* (1), 266-275; (d) Qiu, D.; Zheng, Z.; Mo, F.; Xiao, Q.; Tian, Y.; Zhang, Y.; Wang, J., Gold(III)-Catalyzed Direct Acetoxylation of Arenes with Iodobenzene Diacetate. *Organic Letters* **2011,** *13* (19), 4988-4991; (e) Yoneyama, T.; Crabtree, R. H., Pd(II) catalyzed acetoxylation of arenes with iodosyl acetate. *Journal of Molecular Catalysis A: Chemical* **1996,** *108* (1), 35-40.

3. Tyman, J., Synthetic and natural phenols. Elsevier (Amsterdam The Netherlands and New York): 1996.

4. (a) Chen, M. S.; White, M. C., A predictably selective aliphatic C–H oxidation reaction for complex molecule synthesis. *Science* **2007,** *318* (5851), 783-787; (b) Chen, K.; Baran, P. S., Total synthesis of eudesmane terpenes by site-selective C–H oxidations. *Nature* **2009,** *459* (724), 824-828; (c) Chen, M. S.; White, M. C., Combined effects on selectivity in Fe-catalyzed methylene oxidation. *Science* **2010,** *327* (596), 566-571; (d) Gutekunst, W. R.; Baran, P. S., C–H functionalization logic in total synthesis. *Chemical Society Reviews* **2011,** *40* (4), 1976-1991; (e) Simmons, E. M.; Hartwig, J. F., Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* **2012,** *483* (7387), 70-73; (f) Neufeldt, S. R.; Sanford, M. S.,

Controlling site selectivity in palladium-catalyzed C–H bond functionalization. *Accounts of Chemical Research* **2012,** *45* (6), 936-946; (g) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S., Remarkably high reactivity of Pd $(OAc)_2$–pyridine catalysts: nondirected C–H oxygenation of arenes. *Angewandte Chemie* **2011,** *123* (40), 9581-9584; (h) Zhang, Y.-H.; Yu, J.-Q., Pd (II)-catalyzed hydroxylation of arenes with 1 atm of O_2 or Air. *Journal of the American Chemical Society* **2009,** *131* (41), 14654-14655; (i) Huang, C.; Ghavtadze, N.; Chattopadhyay, B.; Gevorgyan, V., Synthesis of catechols from phenols via Pd-catalyzed silanol-directed C–H oxygenation. *Journal of the American Chemical Society* **2011,** *133* (44), 17630-17633; (j) Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V., Double-Fold C–H oxygenation of arenes Using PyrDipSi: a general and efficient traceless/modifiable silicon-tethered directing group. *Journal of the American Chemical Society* **2012,** *134* (12), 5528-5531; (k) Powers, D. C.; Xiao, D. Y.; Geibel, M. A.; Ritter, T., On the mechanism of palladium-catalyzed aromatic C–H oxidation. *Journal of the American Chemical Society* **2010,** *132* (41), 14530.

5. de Montellano, P. R. O., *Cytochrome P450: structure, mechanism, and biochemistry*. Springer: 2004.

6. Vermerris, W.; Nicholson, R., *Phenolic compound biochemistry*. Springer: 2007.

7. Snook, M. E.; Hamilton, G. A., Oxidation and fragmentation of some phenyl-substituted alcohols and ethers by peroxydisulfate and Fenton's reagent. *Journal of the American Chemical Society* **1974,** *96* (3), 860-869.

8. (a) Derbyshire, D.; Waters, W., An Oxidation Involving the Hydroxyl Cation,$(OH)^+$. **1950**; (b) Vesely, J.; Schmerling, L., Hydrogen Fluroide Catalyzed Hydroxylation of Aromatic Compounds. *The Journal of Organic Chemistry* **1970,** *35* (12), 4028-4033; (c) Kovacic, P.; Kurz, M. E., Friedel-Crafts Oxygenation of Anisole and Alkylbenzenes with Diisopropyl

Peroxydicarbonate1. *Journal of the American Chemical Society* **1965,** *87* (21), 4811-4818; (d) McClure, J. D.; Williams, P. H., Hydrogen Peroxide—Boron Trifluoride Etherate, a New Oxidizing Agent. *Journal of Organic Chemistry* **1962,** *27* (1), 24-26; (e) Tezuka, T.; Narita, N.; Ando, W.; Oae, S., Isomer distribution ratios of phenols in aromatic hydroxylation with the hydroxyl radical generated from α-azohydroperoxide in anhydrous organic media. Comparison with Fenton's reagent. *Journal of the American Chemical Society* **1981,** *103* (11), 3045-3049.

9. Mo, F.; Trzepkowski, L. J.; Dong, G., Synthesis of ortho-Acylphenols through the Palladium-Catalyzed Ketone-Directed Hydroxylation of Arenes. *Angewandte Chemie* **2012,** *124* (52), 13252-13256.

10. Shan, G.; Yang, X.; Ma, L.; Rao, Y., Pd-Catalyzed C–H Oxygenation with TFA/TFAA: Expedient Access to Oxygen-Containing Heterocycles and Late-Stage Drug Modification. *Angewandte Chemie* **2012,** *124* (52), 13247-13251.

11. Ullmann, F.; Elvers, B., *Encyclopedia of industrial chemistry*. VCH: 1991.

12. Khenkin, A. M.; Weiner, L.; Neumann, R., Selective ortho hydroxylation of nitrobenzene with molecular oxygen catalyzed by the H5PV2Mo10O40 polyoxometalate. *Journal of the American Chemical Society* **2005,** *127* (28), 9988-9989.

13. Chen, X.; Zhang, J.; Fu, X.; Antonietti, M.; Wang, X., Fe-g-C3N4-Catalyzed Oxidation of Benzene to Phenol Using Hydrogen Peroxide and Visible Light. *Journal of the American Chemical Society* **2009,** *131* (33), 11658-11659.

14. See Chapter 3.

15. Einhorn, J.; Luche, J.-L.; Demerseman, P., ortho-Hydroxylation of aromatic aldehydes: a short synthesis of 2-hydroxypyrene-1-carbaldehyde. *J. Chem. Soc., Chem. Commun.* **1988,** (20), 1350-1352.

16. Virtamo, J.; Pietinen, P.; Huttunen, J.; Korhonen, P.; Malila, N.; Virtanen, M.; Albanes, D.; Taylor, P.; Albert, P., Incidence of cancer and mortality following α-tocopherol and β-carotene supplementation: a postintervention follow-up. *JAMA: the journal of the American Medical Association* **2003,** *290* (4), 476.

17. Wilkerson, W. W.; Galbraith, W.; DeLucca, I.; Harris, R. R., Topical antiinflammatory dehydroabietylamine derivatives. IV. *Bioorganic & Medicinal Chemistry Letters* **1993,** *3* (10), 2087-2092.

18. Malkowsky, I. M.; Nieger, M.; Kataeva, O.; Waldvogel, S. R., Synthesis and Properties of Optically Pure Phenols Derived from (+)-Dehydroabietylamine. *Synthesis* **2007,** (5), 773.

19. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H., Function-oriented synthesis, step economy, and drug design. *Accounts of Chemical Research* **2007,** *41* (1), 40-49.

20. Cheng, X.; Harzdorf, N. L.; Shaw, T.; Siegel, D., Biomimetic syntheses of the neurotrophic natural products caryolanemagnolol and clovanemagnolol. *Organic Letters* **2010,** *12* (6), 1304-1307.

21. (a) Jursic, B. S.; Martin, R. M., Calculation of bond dissociation energies for oxygen containing molecules by ab initio and density functional theory methods. *International journal of quantum chemistry* **1996,** *59* (6), 495-501; (b) Wang, J.; Tsuchiya, M.; Tokumaru, K.; Sakuragi, H., Intramolecular hydrogen-atom transfer in 2-alkylbenzoyloxyl radicals as studied by transient absorption kinetics and product analyses on the photodecomposition of bis-(2-alkylbenzoyl) peroxides. *Bulletin of the Chemical Society of Japan* **1995,** *68* (4), 1213-1219.

22. Takahara, S. et al. The role of aroyloxyl radicals in the formation of solvent-derived products in photodecomposition of diaroyl peroxides. The reactivity of substituted cyclohexadienyl radicals and intermediacy of ipso intermediates. *Bull. Chem. Soc. Jpn*.**1985**, *58*, 688–697.

22.Yuan, C.; Liang, Y.; Hernandez, T. M.; Berriochoa, A.; Houk, K. N.; Siegel, D. Metal-free Aromatic C-H Oxidation Through a Reverse Rebound Mechanism." *Nature*, in press.

4.7 Experimental section

Safety information

All the peroxides are very dangerous, particularly for phthaloyl peroxide **3.2** and malonoyl peroxide **4.41**. These procedures should be carried out by knowledgeable laboratory workers. And all the reaction conditions should be conducted behind shield. Thermogravimetric analysis (TGA) data showed that phthaloyl peroxide **3.2** was stable below 110 ºC, and which would uncontrollable decompose at above temperature. And the structure related malonoyl peroxide **4.41** decomposed quickly at temperature above 60 ºC. Therefore, all the peroxides should be stored around cool area. The NMR study on the phthaloyl peroxide **3.2**, stored at 0 ºC for half a year, showed no observed decomposition. In order to repeat the reaction result, **it is VERY important to follow the reaction procedure: after the substrates were fully dissolved in HFIP or any given solvent, the peroxide was added in small portions at room temperature.** Neat electro-rich aromatic compounds (e.x.: anisole) reacted uncontrollably with both phthaloyl peroxide **3.2** and malonoyl peroxide **4.41** without solvent. The impure phthaloyl peroxide **3.2** will affect the yield of the reaction significantly. Author recommends recrystallizing **3.2** by benzene/pentane system(the crude was dissolved with benzene at minimum volume at room temperature, then 3-5 equivalent volume of pentane was slowly added to precipitate the solid which was filtered on filtrate funnel to give the white crystal). The best purity of the peroxide should be white needle-like powder. Phthaloyl peroxide **3.2** was not sensitive to the metal spatulas. But author still recommends precaution of metals.

Other necessary safety information can be obtained from the references.

Optimization for phthaloyl peroxide (3.2) mediated hydroxylation of arenes

A borosilicate vial was equipped with a magnetic stir bar and 1,3,5-triisopropylbenzene **4.38** (20 mg, 0.098 mmol). Selected solvent (1.5 mL, 0.026 M) was added by syringe to make homogeneous or heterogeneous solution. To the resulting solution, peroxides (1.3-10 equiv.) were added in one portion and the vial was sealed with a septa screw cap and placed in an oil bath (40 °C). After 18 hours, the reaction crude was cooled and the solvent was evaporated by a steam of N_2 flow. The crude was upon for further NMR analysis. The final optimized condition is entry 20.

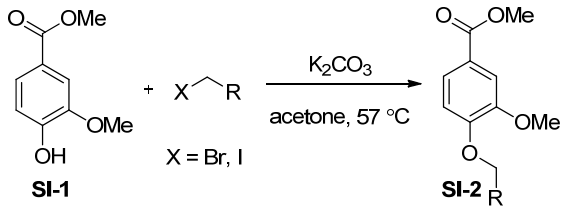
Reason of this choice:

Based on our observation on the common solvents entry 1-10, we found only the chlorinated solvent delivered the product in low yield (<40%). Expanded investigation showed hexafluoroisopropanol (HFIP) promoted the yield to 97%. In order to understand the generality

of the hydroxylation process with different peroxides, a screen of other peroxides showed that only the malonyl peroxide **4.41** had comparable reactivity. There are three reasons that determine the choice of phthaloyl peroxide **3.2**. First, after thermogravimetric analysis (TGA) of the two unique peroxides, we found the phthaloyl peroxide **3.2** was stable at relative low temperature (< 100 °C) in contrast to the decomposing file (50% weight loss at 60 °C) of malonyl peroxide **4.41** (details in **TGA data**). Second we also observed diminished reactivity of malonyl peroxide **4.41** with substrates in the paper. Moreover, it is easy to synthesize **3.2** with cheap materials (Aldrich: phthaloyl chloride: 28.2 $/100g, sodium percarbonate: 5 $/100g) at reasonable scale (1-5 g phthaloyl peroxide **3.2** after recrystallization) in one single step. Further optimization using phthaloyl peroxide **3.2** showed the best result can be obtained by using a slight excess of **3.2** (1.3 equiv.).

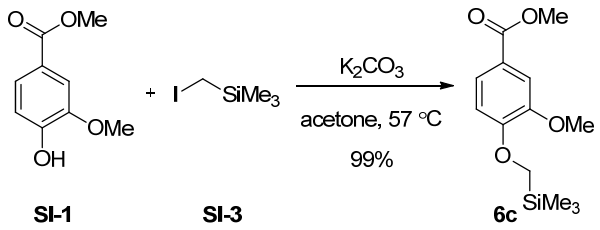
Synthesis of substrates:

General procedure for functionalization of methyl vinillate:



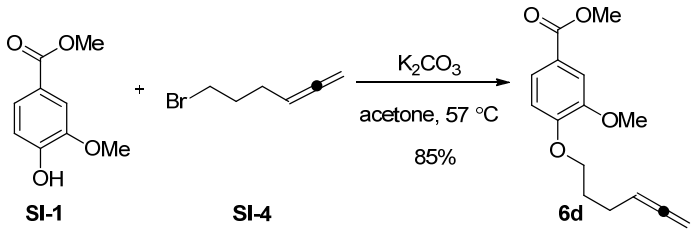
A 100 mL flask with a Teflon-coated stir bar was charged with methyl vinillate **SI-1** (1.0 equiv.), K_2CO_3 (2.5 equiv.) and bromo/iodo compound RCH_2X (2.0 equiv.). To the mixture, acetone (10-20 mL) was added to generate a suspension. A cold-water cooled condenser was connected to the flask and which was immersed into a 70 ºC oil bath. Upon complete consumption of the methyl vinillate (as determined by TLC, 12-36 h), the reaction mixtures was diluted with 50 mL Et_2O, and filtered through a glass filtrate. The crude material was concentrated and purified by silica gel column chromatography to afford the desired product.

Substrate scope-characterization:



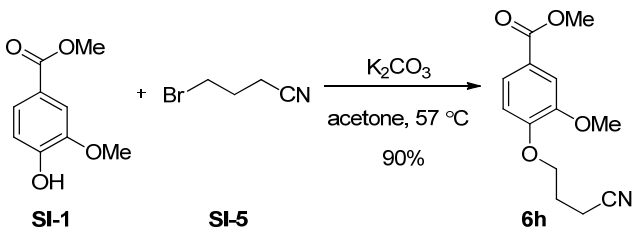
SI-1 SI-3 6c

6c: Prepared from the general procedure using methyl vinillate **SI-1** (0.50 g, 2.7 mmol) in acetone (10 mL). After 10 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to give **6c** (0.73 g, 99%) as white solid. m.p.: 54.5-55.3 °C; TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.65; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 p.p.m. (dd, J = 2.0 and 8.8 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 3.88 (s, 6H), 3.71 (s, 2H), 0.16 (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.0, 155.3, 149.0, 123.6, 122.0, 112.8, 111.1, 62.2, 56.2, 51.9, -2.9; IR (KBr): 2955, 1717, 1293, 1261 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{21}O_4Si$, 269.12091; found, 269.12043.



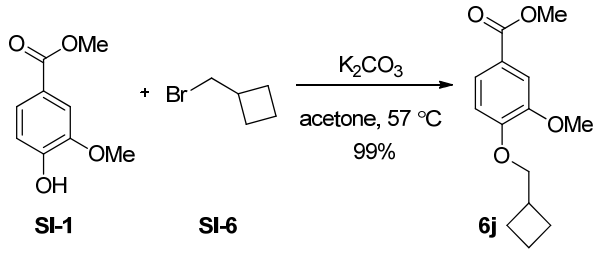
SI-1 SI-4 6d

6d: Prepared from the general procedure using methyl vinillate **SI-1** (1.0 g, 1.6 mmol) in acetone (17.5 mL). After 36 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (20/1 → 10/1 hexanes/EtOAc, v/v) to give **6d** (1.22 g, 85%) as white crystalline solid. m.p.: 51.5-52.3 °C; TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 p.p.m. (dd, J = 2.0 and 8.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 5.16 (penta, J = 6.4 Hz, 1H), 4.69 (penta, J = 3.2 Hz, 2H), 4.11 (t, J = 6.4 Hz, 2H) 3.91 (s, 3H), 3.89 (s, 3H), 2.23-2.17 (m, 2H), 2.00 (penta, J = 6.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.5, 166.8, 152.4, 148.8, 123.4, 122.4, 112.2, 111.4, 89.0, 75.4, 68.1, 56.0, 51.9, 28.1, 24.4; IR (KBr): 2950, 1955, 1716, 1600 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{19}O_4$, 263.1283; found, 263.1284.



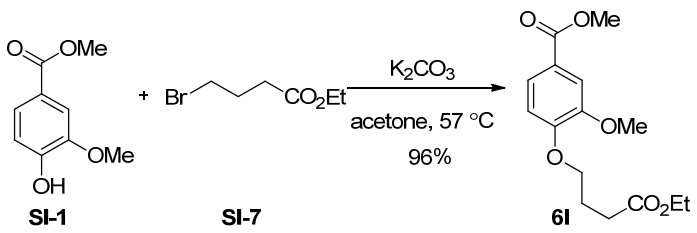
SI-1 **SI-5** **6h**

6h: Prepared from the general procedure using methyl vinillate **SI-1** (0.47 g, 2.6 mmol) in acetone (10 mL). After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to give **6h** (0.58 g, 90%) as white crystalline solid. m.p.: 60.0-62.0 °C; TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 p.p.m. (dd, J = 2.0 and 8.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 6.88 (J = 8.4 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.20 (penta, J = 6.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7, 151.7, 149.0, 123.4, 119.1, 112.4, 112.1, 66.4, 55.9, 52.0, 25.3, 14.1; IR (KBr): 2953, 2246, 1710, 1273 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NNaO_4$, 272.08933; found, 272.08940.

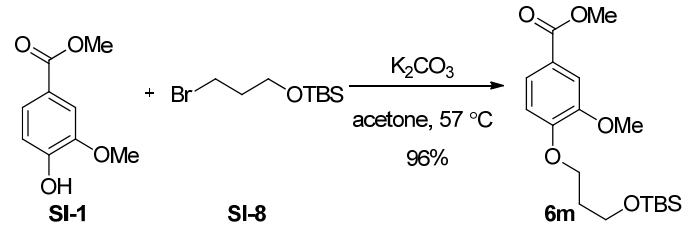


SI-1 **SI-6** **6j**

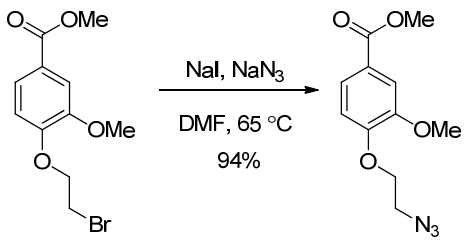
6j: Prepared from the general procedure using methyl vinillate **SI-1** (0.50 g, 2.7 mmol) in acetone (15 mL). After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to give **6j** (0.68 g, 99%) as white crystalline solid. m.p.: 58.5-60.5 °C; TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 p.p.m. (dd, J = 1.6 and 8.4 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 6.8 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.86 (hepta, J = 3.6 Hz, 1H), 2.13-2.20 (m, 2H), 1.82-2.04 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.9, 152.8, 148.9, 123.5, 122.4, 112.5, 111.7, 73.2, 56.1, 51.9, 34.4, 25.1, 18.6; IR (KBr): 2949, 1716, 1271 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{19}O_4$, 251.1283; found, 251.1283.



6l: Prepared from the general procedure using methyl vinillate **SI-1** (0.50 g, 2.7 mmol) in acetone (10 mL). After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (20/1 → 10/1 hexanes/EtOAc, v/v) to give **6l** (0.78 g, 96%) as colorless oil. TLC (hexanes/EtOAc, 4/1 v/v): RF = 0.70; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 p.p.m. (dd, J = 2.0 and 8.4 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 6.88 (J = 8.4 Hz, 1H), 4.09-4.16 (m, 4H), 3.90 (s, 3H), 3.89 (s, 3H), 2.53 (t, J = 6.4 Hz, 2H), 2.17 (penta, J = 6.4 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0, 166.9, 152.2, 148.9, 123.5, 122.7, 112.3, 111.5, 67.7, 60.5, 56.0, 52.0, 30.6, 24.3, 14.2; IR (KBr): 2954, 1724, 1672, 1284 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}NaO_6$, 319.11521; found, 319.11505.

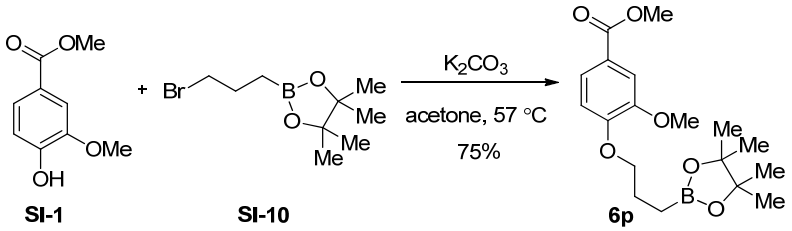


6m: Prepared from the general procedure using methyl vinillate **SI-1** (1.5 g, 8.2 mmol) in acetone (20 mL). After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to give **6m** (2.8 g, 96%) as colorless oil. TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.43; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 p.p.m. (ddd, J = 0.8, 2.0 and 7.6 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 6.90 (J = 7.6 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.80 (t, J = 6.0 Hz, 2H), 2.02 (dpenta, J = 0.8 and 6.0 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.9, 152.6, 148.8, 123.5, 122.3, 112.2, 111.3, 65.6, 59.3, 55.9, 51.9, 32.0, 25.8, 18.2, -5.5; IR (KBr): 2953, 1720, 1106 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{31}O_5Si$, 355.1941; found, 355.1942.



SI-9 6n

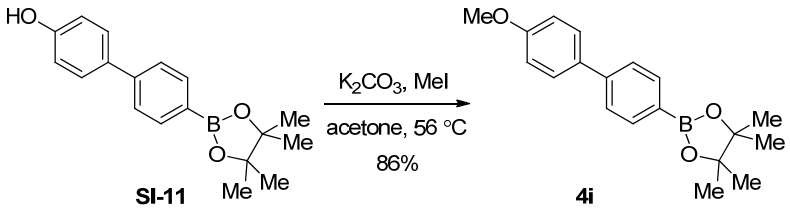
6n: **SI-9 (**0.27 g, 0.93 mmol, 1.0 equiv.**)** was dissolved in DMF (5 mL), added solid NaI (0.28 g, 1.9 mmol, 2.0 equiv.) and NaN_3 (0.12 g, 1.9 mmol, 2.0 equiv.) in sequence. The flask was immersed in a 66 °C oil bath for 24 hours. The reaction was cooled and quenched with aqueous saturated NH_4Cl solution (20 mL). The crude was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to afford off-white solid **6n** (0.22 g, 94%). m.p.: 47.0-48.5 °C; TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.40; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 p.p.m. (dd, J = 2.0 and 8.4 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 6.88 (J = 8.4 Hz, 1H), 4.22 (t, J = 4.2 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.67 (t, J = 4.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7, 151.6, 149.1, 123.6, 123.3, 112.6, 112.2, 67.7, 56.0, 52.0, 50.0; IR (KBr): 2951, 2111, 1715, 1272 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}N_3O_4$, 252.0984; found, 252.0987.



SI-1 SI-10 6p

6p: Prepared from the general procedure using methyl vinillate **SI-1** (0.30 g, 1.6 mmol) in acetone (7.5 mL). After 36 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 5/1 hexanes/EtOAc, v/v) to give **6p** (0.43 g, 75%) as white amorphous solid. m.p.: 64.5-65.1 °C; TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 p.p.m. (dd, J = 2.0 and 8.4 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.05 (t, J = 3.2 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.96 (penta, J = 7.6 Hz, 2H), 1.23 (s, 12H), 0.87-0.96 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.9, 152.6, 148.8, 123.5, 122.2, 112.2, 111.4, 83.1, 70.4, 56.0, 51.9, 24.8, 23.3; IR (KBr): 2977, 1716, 1600, 1514 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{18}H_{27}O_6{}^{11}B$, 350.1901; found, 350.1901.

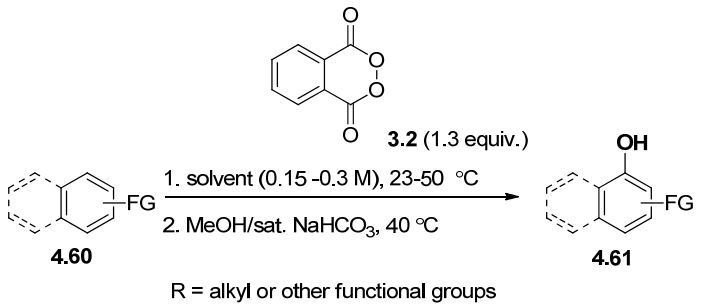
Procedure for synthesis of 4-Bpin-4'-methoxy-biphenyl **4i**:



4i: To the solution of **SI-11** (0.58 g, 1.96 mmol, 1.0 equiv.) in acetone (10 mL), potassium carbonate (0.81 g, 5.9 mmol, 3.0 equiv) and methyl iodine (0.24 mL, 3.9 mmol, 2.0 equiv) were added. The flask was immersed into a 70 °C oil bath for 36 hours. The flask was cooled to 23 °C and poured into Et_2O (50 mL). The crude was filtered and concentrated to pale yellow paste which was purified by silica gel column chromatography (100/1 → 10/1 hexanes/EtOAc, v/v) to give **4i** (0.50 g, 86%) as white solid. m.p. 140-142 ºC; TLC (hexanes/EtOAc, 20/1 v/v): RF = 0.25; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.87 p.p.m. (dd, J = 2.0 and 8.4 Hz, 2H), 7.59-7.56 (m, 4H), 6.99 (dd, J = 2.0 and 6.8 Hz, 2H), 3.86 (s, 3H), 1.37 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.4, 143.4, 135.2, 133.4, 128.2, 126.0, 114.2, 83.7, 55.3, 24.9; IR (KBr): 3408, 1975, 1607 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{19}H_{23}{}^{11}BO_3$, 310.1740; found, 310.1754.

Phthaloyl peroxide 3.2 mediated oxidation of arenes to phenols:

General procedure A- Hydroxylation of arenes on small scale:



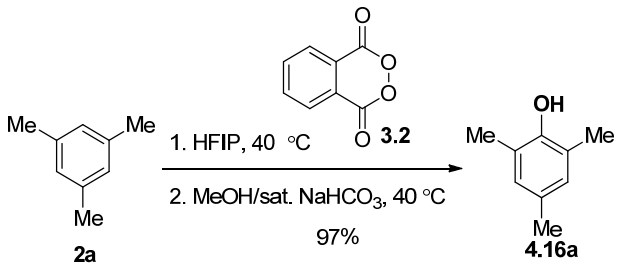
A borosilicate vial was equipped with a magnetic stir bar and corresponding arenes **4.60** (0.2-0.8 mmol). HFIP or TFE (2-5 mL, 0.1-0.3 M) was added by syringe to make homogeneous solution. In some cases, to assist dissolving the arenes, certain volume of $DCCl_3$ was added. To the resulting solution, phthaloyl peroxide **3.2** (1.3 equiv.) was added in small portions and the vial was sealed with a septa screw cap and placed in an oil bath (23-50 °C). After 3-24 hours, the reaction crude was cooled and the solvent was evaporated by a steam of N_2 flow or by vacuum. Under a stream of N_2, MeOH (3 mL) and saturated $NaHCO_3$ solution (0.2 mL) was added and the vial was swiftly sealed with septa screw cap and parafilm. After a certain period of time, the reaction crude was either (i) quenched with pH 7 buffer (5 mL) and extracted with EtOAc or Et_2O (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4, filtered and concentrated or (ii) concentrated directly onto silica *in vacuo*. The crude material was then purified by silica gel column chromatography using the noted mixed solvent to gain the desired phenolic product **4.61**.

General procedure B- Hydroxylation of arenes on large scale:

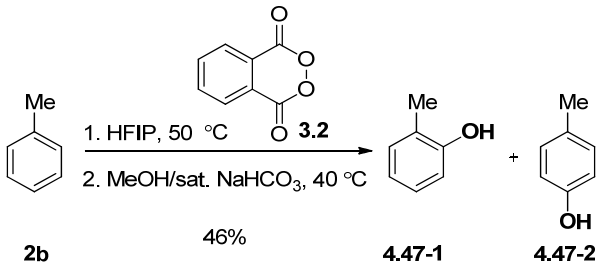
Precaution: The reaction should be presented by experienced research assistant under full protective equipment. A 250 mL flask was equipped with a magnetic stir bar and corresponding arenes **4.60** (10-30 mmol). HFIP or TFE (50-200 mL, 0.2-0.4 M) was added by syringe to make homogeneous solution. To the resulting solution, phthaloyl peroxide **3.2** (1.3 equiv.) was added in small portions in 10 min and the flask was capped with a septa and placed in an oil bath (23-55 °C). After a certain period of time, the reaction crude was cooled and 0.05 mL of the crude was taken and concentrated for NMR analysis *to assure the fully consumption of phthaloyl peroxide **3.2***. Bulb to bulb distillation was setup to distill off the solvent in a 90 °C oil bath. After the distillation, the flask is cooled, MeOH (100-200 mL) and saturated $NaHCO_3$ soution (10-20 mL) were added and the flask was sealed with a septum with a N_2 balloon and the flask was immersed in an oil bath under certain temperature. After a certain period of time, the

reaction crude was quenched with pH 7 buffer (150 mL) and extracted with EtOAc (50 mL × 3), and the combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using the noted mixed solvent to gain the desired phenolic product **4.61**.

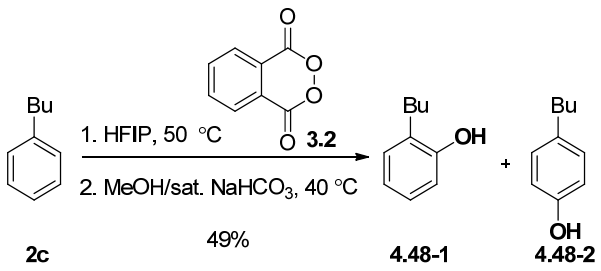
Substrate scope-characterization (Table 2)**:**



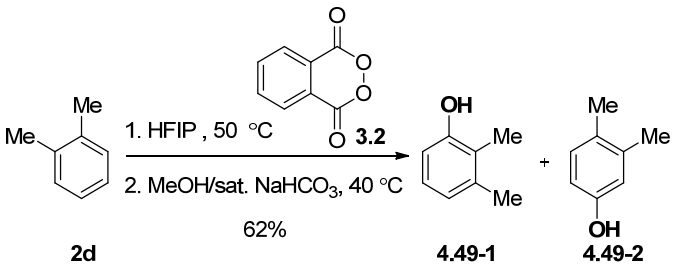
2,4,6-Trimethylphenol **4.16a**: Prepared from general procedure A using mesitylene **2a** (50 mg, 0.42 mmol) and HFIP (2.5 mL) at 40 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was directly purified by silica gel column chromatography (20/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.16a**(55.0 mg, 97%). The spectrums match the commercial sources.



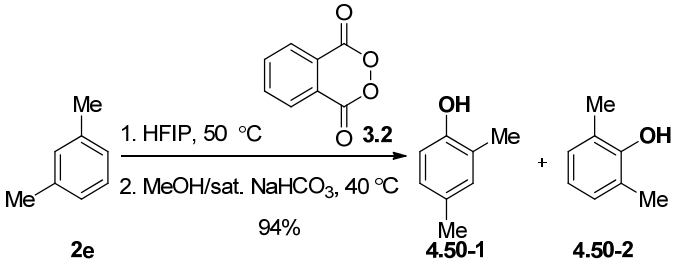
o-Cresol **4.47-1** and *p*-cresol **4.47-2**: Prepared from general procedure A using toluene **2b** (50 mg, 0.54 mmol) and HFIP (2.5 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.47-1** and **4.47-2** (26.9 mg, 46%, **4.47-1** : **4.47-2** = 1:1). The spectrums match the commercial sources.



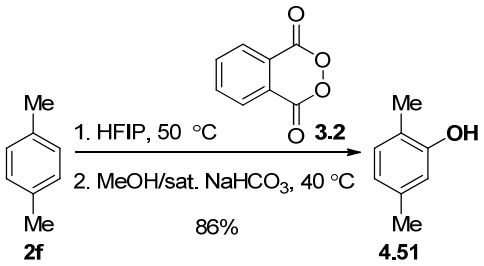
2-Butylphenol **4.48-1** and 4-butylphenol **4.48-2**: Prepared from general procedure A using *n*-butyl benzene **2c** (70 mg, 0.52 mmol) and HFIP (2.5 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.48-1** and **4.48-2** (38.0 mg, 49%, **4.48-1** : **4.48-2** = 1:1). The spectrums match the commercial sources.



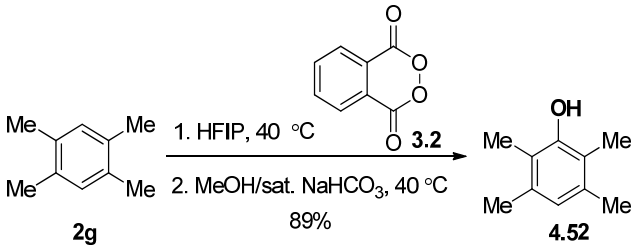
2,3-Dimethylphenol **4.49-1** and 3,4-dimethylphenol **4.49-2**: Prepared from general procedure A using *o*-xylene **2d** (50 mg, 0.47 mmol) and HFIP (2 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.49-1** and **4.49-2** (35.5 mg, 62%, **4.49-1** : **4.49-2** = 2.1:1). The spectrums match the commercial sources.



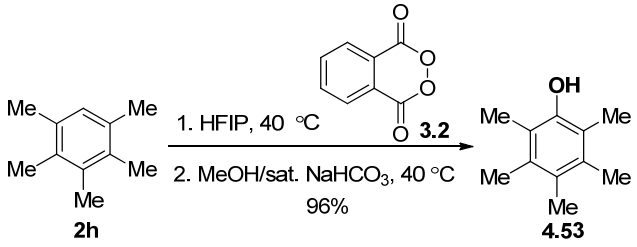
2,4-Dimethylphenol **4.50-1** and 2,6-dimethylphenol **4.50-2**: Prepared from general procedure A using *m*-xylene **2e** (50 mg, 0.47 mmol) and HFIP (2.5 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.50-1** and **4.50-2** (53.9 mg, 94%, **4.50-1** : **4.50-2** = 6.1:1). The spectrums match the commercial sources.



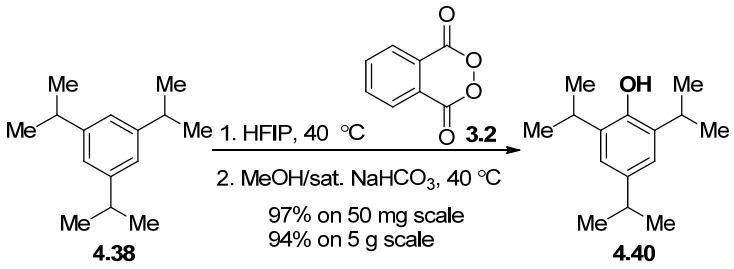
2,5-Dimethylphenol **4.51**: Prepared from general procedure A using *p*-xylene **2f** (50 mg, 0.47 mmol) and HFIP (2 mL) at 40 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.51** (49.2 mg, 86%). The spectrums match the commercial sources.



2,3,5,6-Tetramethylphenol **4.52**: Prepared from general procedure A using 1,2,4,5-tetramethylbenzene **2g** (70 mg, 0.52 mmol) and HFIP (2.5 mL) at °C. After 10 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (20/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.52** (70.0 mg, 89%). The spectrums match the commercial sources.



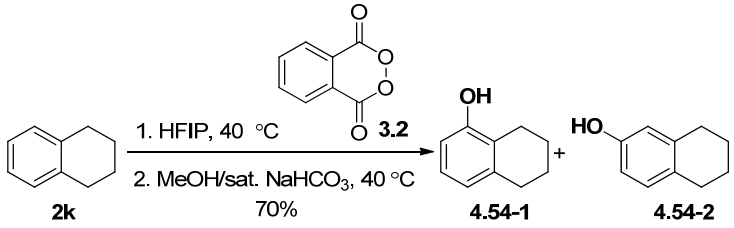
2,3,4,5,6-Pentamethylphenol **4.53**: Prepared from general procedure A using 1,2,3,4,5-pentamethylbenzene **2h** (80 mg, 0.54 mmol) and HFIP (2.5 mL) at 40 °C. After 8 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.53** (85 mg, 96%). The spectrums match the commercial sources.



2,4,6-Triisopropylphenol **4.40**: Prepared from general procedure A using 1,3,5-triisopropylbenzene **4.38** (50 mg, 0.25 mmol) and HFIP (2 mL) at 40 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.40** (52.5 mg, 97%). The spectrums match the commercial sources.

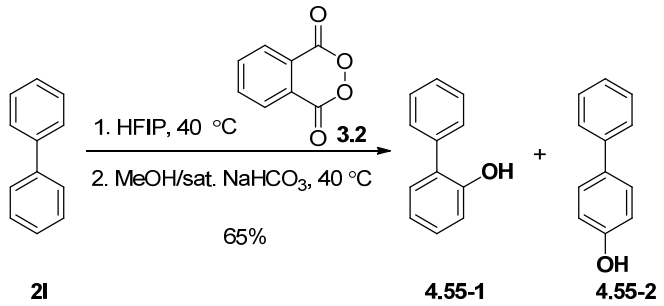
Large scale:

2,4,6-Triisopropylphenol **4.40**: Prepared from general procedure B using **4.38** (5.0 g, 24.4 mmol) and HFIP (100 mL) at 40 °C. After 36 hours, HFIP (92 mL) was recovered after bulb to bulb distillation. It should be notice that to hydrolyze the crude, MeOH (200 mL) and saturated K_2CO_3 solution (10 mL) was added and flask was immersed in a 70 °C oil bath for 48 hours. The reaction crude was quenched with pH 7 buffer (150 mL) and extracted with EtOAc (50 mL × 3), and the combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4, filtered and concentrated. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.40** (5.05 g, 94%) as yellow oil.

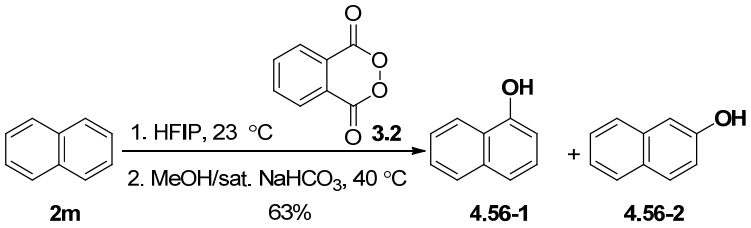


5,6,7,8-Tetrahydro-1-naphthol **4.54-1** and 5,6,7,8-tetrahydro-2-naphthol **4.54-2**: Prepared from general procedure A using 1,2,3,4-tetrahydronaphthalene **2k** (70 mg, 0.53 mmol) and HFIP (2.5 mL) at 40 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title

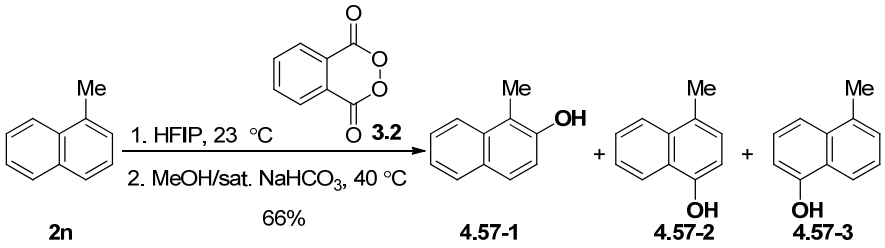
compounds **4.54-1** and **4.54-2** (55.2 mg, 70%, **4.54-1** : **4.54-2** = 1.5:1). The spectrums match the commercial sources.



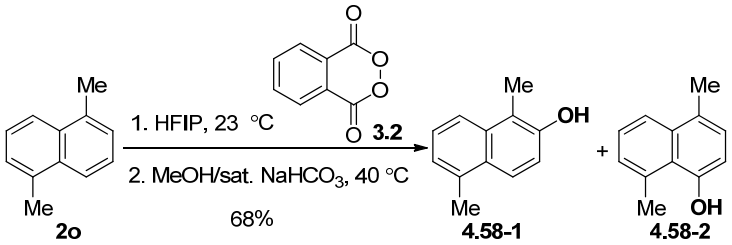
2-Hydroxybiphenyl **4.55-1** and 4-hydroxybiphenyl **4.55-2**: Prepared from general procedure A using biphenyl **2l** (70 mg, 0.45 mmol) and HFIP (2.5 mL) at 40 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford biphenyl **2l** (17.1 mg, 24%) and the title compounds **4.55-1** and **4.55-2** (49.9 mg, 65%, **4.55-1** : **4.55-2** = 2.5:1). The spectrums match the commercial sources.



1-Naphthol **4.56-1** and 2-naphthol **4.56-2**: Prepared from general procedure A using naphthalene **2m** (70 mg, 0.55 mmol) and HFIP (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.56-1** and **4.56-2** (49.3 mg, 63%, **4.56-1** : **4.56-2** = 5.8:1). The spectrums match the commercial sources.



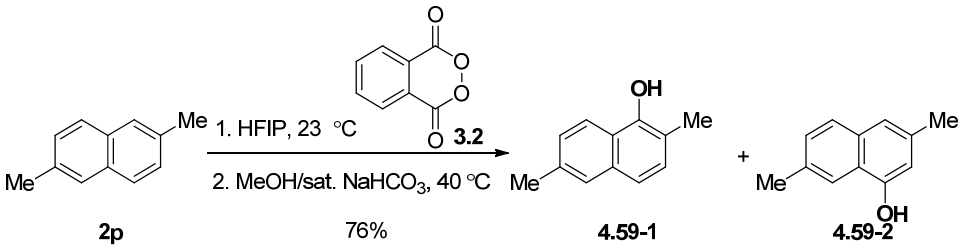
1-Methyl-2-naphthol **4.57-1**, 4-methyl-1-naphthol **4.57-2** and 5-methyl-1-naphthol **4.57-3**: Prepared from general procedure A using 1-methylnaphthlene **2n** (70 mg, 0.49 mmol) and HFIP (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds **4.57-1**, **4.57-2** and **4.57-3** (45.9 mg, 66%, **4.57-1** : **4.57-2** : **4.57-3** = 1.4:2:1). The spectrums match the commercial sources and reported spectrum.



3,8-Dimethyl-1-naphthol **4.58-1** and 4,8-dimethyl-1-naphthol **4.58-2**: Prepared from general procedure A using 1,5-dimethylnaphthlene **2o** (80 mg, 0.51 mmol) and HFIP (3 mL) at 23 °C. After 8 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compound **4.58-1** (30.9 mg, 35%) and **4.58-2** (20.8 mg, 33%).

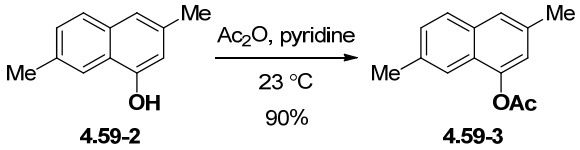
3,8-Dimethyl-1-naphthol **4.58-1**: m.p.: 154.0-157.0 °C; TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.49; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 p.p.m. (d, J = 8.8 Hz, 2H), 7.39 (t, J = 8.8 Hz, 1H), 7.19 (d, J = 6.0 Hz, 1H), 7.10 (d, J = 6.0 Hz, 1H), 4.90 (s, 1H), 2.67 (s, 3H), 2.55 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.2, 134.8, 134.0, 128.2, 126.1, 124.1, 123.4, 121.6, 117.0, 115.7, 19.7, 10.7; IR (KBr): 3270, 1384 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{12}O$, 172.0888; found, 172.0888.

4,8-Dimethyl-1-naphthol **4.58-2**: m.p.: 87.0-89.6 °C; TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 p.p.m. (dd, J = 0.8 and 8.4 Hz, 1H), 7.38 (dt, J = 0.8 and 8.4 Hz, 1H), 7.23 (dt, J = 0.8 and 7.2 Hz, 1H), 7.10 (dd, J = 0.8 and 7.2 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.25 (brs, 1H), 2.97 (s, 3H), 2.59 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.4, 135.4, 134.9, 128.0, 126.8, 126.1, 125.8, 123.9, 122.4, 109.6, 25.0, 19.7; IR (KBr): 3255, 1591, 1384 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}O$, 173.0966; found, 173.0966.



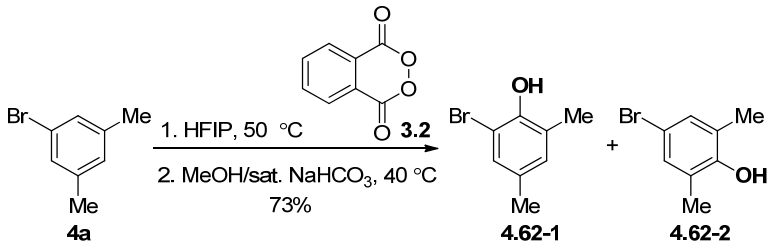
2,6-Dimethyl-1-naphthalenol **4.59-1** and 3,7-dimethyl-1-naphthalenol **4.59-2**: Prepared from general procedure A using 2,6-dimethylnaphthlene **2p** (80 mg, 0.51 mmol) and HFIP (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford **4.59-1** (66.1 mg, 68%) and **4.59-2** (6.1 mg, 8%).

2,6-Dimethyl-1-naphthalenol **4.59-1**: m.p.: 105.9-108.9 °C; TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.59; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 p.p.m. (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.30 (dd, J = 1.6 and 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 5.13 (s, 1H), 2.50 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.5, 134.9, 133.7, 129.0, 127.5, 126.6, 122.4, 120.7, 119.5, 115.3, 21.6, 15.6; IR (KBr): 3424, 1277,1250 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}O$, 173.0966; found, 173.0967.

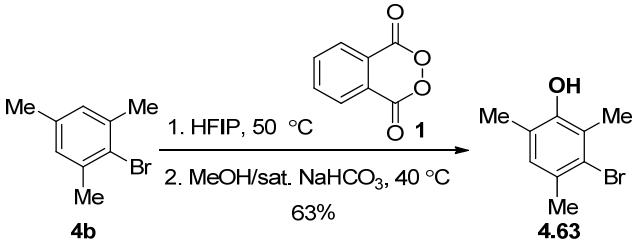


4.59-3: To 3,7-dimethyl-1-naphthalenol **4.59-2** (6.1 mg, 0.040 mmol), pyridine (0.4 mL) and acetic anhydride (0.5 mL) were added at 23 ºC. After 14 hours, the volatile was removed under reduced pressure. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.59-3** (7.6 mg, 90%). The total two-steps yield is 7%.

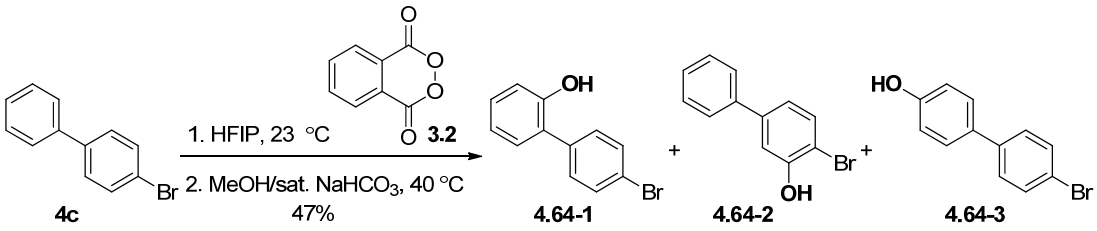
4.59-3: TLC (hexanes/EtOAc, 15/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 p.p.m. (d, J = 8.4 Hz, 1H), 7.57-7.50 (m, 1H), 4.46 (s, 1H), 7.27 (dd, J = 1.6 and 8.4 Hz, 1H), 7.04 (d, J = 1.6 Hz, 1H), 2.48 (s, 3H), 2.47 (s, 3H), 2.45 (s. 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.7, 145.9, 135.3, 134.4, 133.1, 128.8, 127.3, 125.1, 124.9, 120.2, 119.8, 21.9, 21.6, 21.1; IR (KBr): 3390, 1768, 1203 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{14}O$, 214.0994; found, 214.0995.



4.62-1 and **4.62-2**: Prepared from general procedure A using 5-bromo-*m*-xylene **4a** (100 mg, 0.54 mmol) and HFIP (3 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford the title compounds **4.62-1** (68.3 mg, 63%) and **4.62-2** (11.1 mg, 10%). The spectrums match commercial sources.



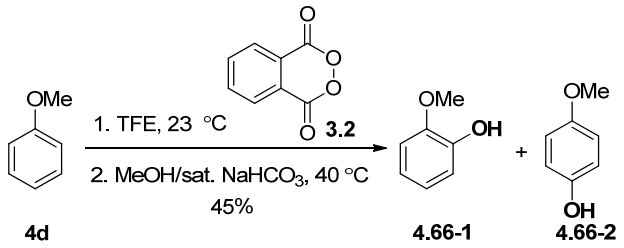
4.63: Prepared from general procedure A using mesityl bromide **4b** (100 mg, 0.50 mmol) and HFIP (3 mL) at 50 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.63** (68.1 mg, 63%) as pale yellow solid. The spectrums match commercial sources.



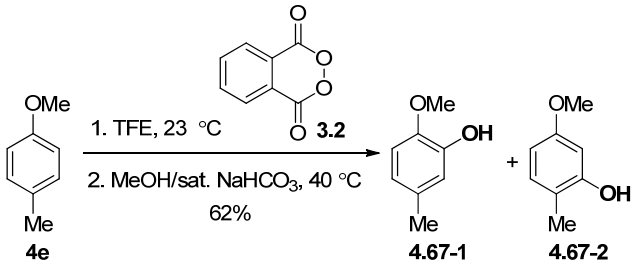
4.64-1, **4.64-2** and **4.64-3**: Prepared from general procedure A using **4c** (110 mg, 0.47 mmol) and HFIP (3 mL) at 23 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the **4c** (33.2 mg, 30%) and mixtures of **4.64-1** and **4.64-2** (42.5 mg, 36%, **4.64-1** : **4.64-2** =1:1), and **4.64-3** (19.8mg, 17%). The spectrum of **4.64-3** matches the commercial sources. Preparation scale TLC separated **4.64-1** (16.6 mg, 15%) and **4.64-2** (16.5 mg, 15%).

4.64-1: m.p.: 190-192 °C, TLC (pentane/Et_2O, 10/1 v/v): RF = 0.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63-7.59 p.p.m. (m, 2H), 7.39-7.36 (m, 2H), 7.29-7.21 (m, 2H), 7.0 (dt, J = 1.2 and 8.0 Hz, 1H), 6.96 (dd, J = 1.2 and 8.0 Hz, 1H), 5.01 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.2, 136.1, 132.2, 130.8, 130.2, 129.4, 127.0, 122.0, 121.1, 116.0; IR (KBr): 3433, 1384 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{10}O^{81}Br$, 250.9895; found, 250.9899.

4.64-2: m.p.: 180-183 °C, TLC (pentane/Et_2O, 10/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52-7.47 p.p.m. (m, 2H), 7.44-7.40 (m, 3H), 7.17 (d, J = 1.6 Hz, 1H), 7.13 (dd, J = 1.6 and 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 5.27 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.2, 136.0, 131.3, 129.5, 128.9, 128.3, 127.1, 124.0, 122.1, 119.1; IR (KBr): 3411, 1632 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{12}H_{10}O^{81}Br$, 250.9895; found, 250.9898.

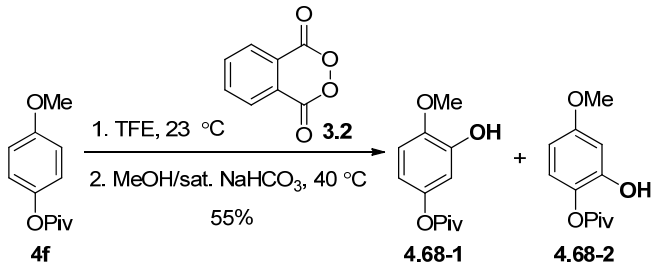


4.66-1 and **4.66-2**: Prepared from general procedure A using anisole **4d** (60 mg, 0.55 mmol) and TFE (3 mL) at 23 °C. After 14 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O, v/v) to afford the title compounds (31.2 mg, 45%, **4.66-1** : **4.66-2** =1.4:1). The spectrums match the commercial sources.



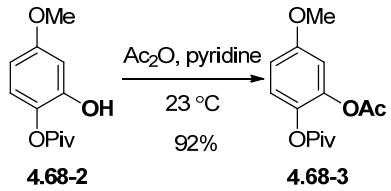
4.67-1 and **4.67-2**: Prepared from general procedure A using 4-methyl anisole **4e** (65 mg, 0.53 mmol) and TFE (3 mL) at 23 °C. After 16 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 pentane/Et_2O,

v/v) to afford **4e** (12.1 mg, 19%) and title compounds (45.8 mg, 62%, **4.67-1** : **4.67-2** =1.1:1). The spectrums match the commercial sources.



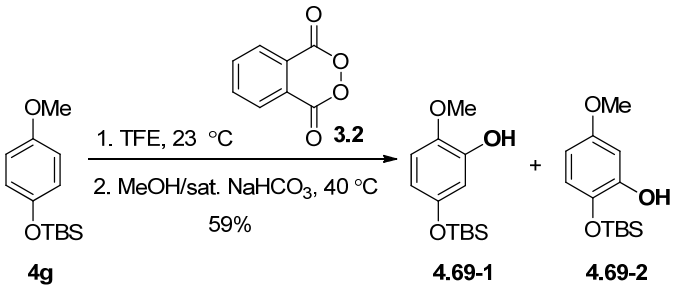
4.68-1 and **4.68-2**: Prepared from general procedure A using 2,2-dimethyl-propanoic acid 4-methoxyphenyl ester **4f** (100 mg, 0.48 mmol) and TFE (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 2/1 pentane/Et_2O, v/v) to afford **4f** (10.0 mg, 10%), **4.68-1** (43 mg, 40%) and **4.68-2** (16.4 mg, 15%).

4.68-1: TLC (pentane/Et_2O, 2/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.81 p.p.m. (d, J = 8.8 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 2.4 and 8.8 Hz, 1H), 5.69 (s, 1H), 3.89 (s, 3H), 1.33 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.3, 146.1, 145.1, 144.3, 112.4, 110.5, 108.5, 56.2, 39.0, 27.1; IR (KBr): 3436, 2971, 1749, 1508 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{17}O_4$, 225.1127; found, 225.1125.



4.68-3: To **4.68-2** (16.4 mg, 0.073 mmol), pyridine (0.4 mL) and acetic anhydride (0.5 mL) were added. After 14 hours, the volatile was removed under reduced pressure. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4.68-3** (18.0 mg, 92%). The total two-steps yield is 14%.

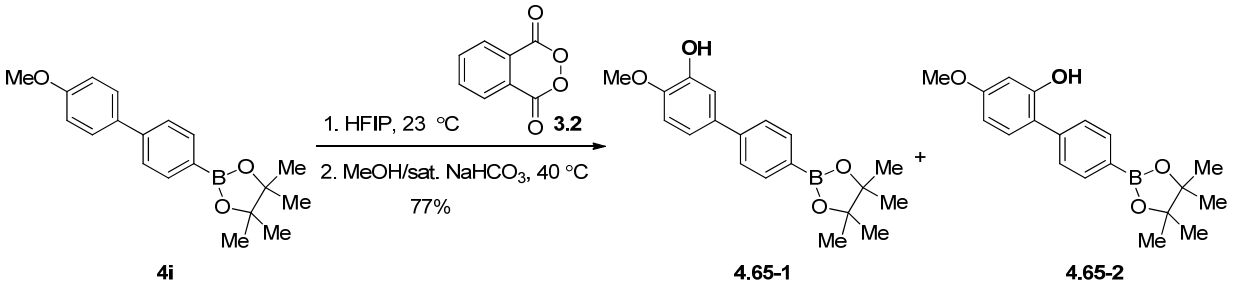
4.46-3: TLC (hexanes/EtOAc, 4/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.04 p.p.m. (d, J = 9.2 Hz, 1H), 6.77 (dd, J = 2.8 and 9.2 Hz, 1H), 6.72 (d, J = 2.8 Hz, 1H), 3.79 (s, 3H), 2.26 (s, 3H), 1.34(s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.3, 168.1, 157.5, 142.5, 135.9, 123.6, 111.9, 109.0, 55.7, 39.1, 27.1, 20.7; IR (KBr): 3498, 1751, 1740 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{18}NaO_5$, 289.10464; found, 289.10454.



4.69-1 and **4.69-2**: Prepared from general procedure A using tert-butyl(4-methoxyphenoxy)dimethylsilane **4g** (120 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 4 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4.69-1** (52.2 mg, 41%) and **4.69-2** (22.9 mg, 18%).

4.69-1: TLC (hexanes/EtOAc, 2/1 v/v): RF = 0.75; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 p.p.m. (d, J = 8.8 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 6.31 (dd, J = 2.8 and 8.8 Hz, 1H), 5.57 (s, 1H), 3.84 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.1, 146.0, 141.3, 111.1, 110.7, 107.2, 56.4, 25.7, 18.2, -4.5; IR (KBr): 3447, 1627, 1507 cm^{-1}; HRMS (*m*/*z*): $[M-H]^-$ calcd for $C_{13}H_{21}O_3Si$, 253.12654; found, 253.12642.

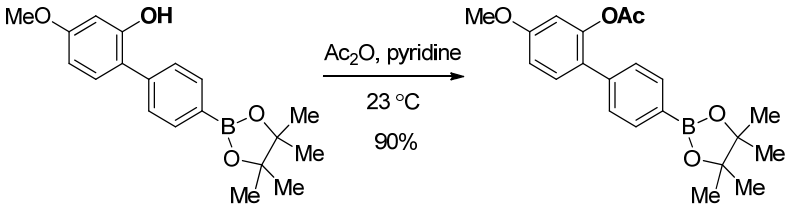
Procedure for characterization of **4.69-2**: To **4.69-2** (22.9 mg, 0.09 mmol, 1.0 equiv.) in THF (1 mL), TBAF (0.10 mL, 1 mol/L, 1.1 equiv.) was slowly added at room temperature. After 1 hour, saturated NH_4Cl solution (5 mL) was added into the solution. The crude was extracted with Et_2O (10 mL × 3) and the combined organic solution was washed with brine, then dried on Na_2SO_4. The crude was filtered and concentrated to afford 4-methoxycatechol and the spectrum matches the commercial source.



Pinacol phenol **4.65-1** and pinacol phenol **4.65-2**: Prepared from general procedure A using **4i** (100 mg, 0.32 mmol) and HFIP (3 mL) at 23 °C. After 8 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1

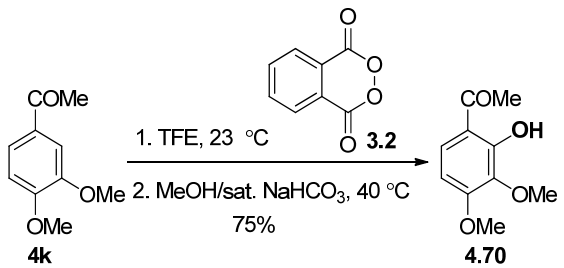
hexanes/EtOAc, v/v) to afford the title compounds **4.65-1** and **4.65-2** (81.1 mg, 77%, **4.65-1** : **4.65-2** =2:1).

4.65-1: m.p.: 117-119 °C, TLC (CH_2Cl_2/MeOH, 100/1 v/v): RF = 0.65; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 p.p.m. (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 2.0 and 8.4 Hz, 2H), 7.22 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 2.0 and 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.64 (s, 1H), 3.93 (s, 3H), 1.36 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.4, 145.8, 143.4, 135.2, 134.5, 126.0, 118.9, 113.4, 110.8, 83.8, 56.0, 24.9; IR (KBr): 3408, 1361 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{19}H_{24}{}^{11}BO_4$, 328.17983; found, 328.17931.



4.65-3: To the compound **4.65-2** (13.0 mg, 0.040 mmol), pyridine (0.4 mL) and acetic anhydride (0.5 mL) were added at 23 ºC. After 10 hours, the volatile was removed under reduced pressure. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.65-3** (13.2 mg, 90%).

4.43-3: TLC (CH_2Cl_2/MeOH, 100/1 v/v): RF = 0.49; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.83 p.p.m. (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 6.87 (dd, J = 2.5 and 8.5 Hz, 1H), 6.69 (d, J = 2.5 Hz, 1H), 3.84 (s, 3H), 2.09 (s, 3H), 1.36 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.2, 159.9, 148.5, 140.4, 134.7, 131.3, 128.1, 112.4, 108.5, 83.8, 55.6, 29.7, 24.9, 20.9; IR (KBr): 3427, 1764, 1360 cm^{-1}; HRMS (m/z): $[M+Na]^+$ calcd for $C_{19}H_{23}BNaO_4$, 349.15857; found, 349.15869.

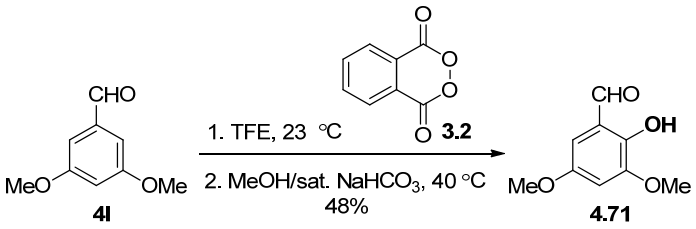


4.70: Prepared from general procedure A using 3,4-dimethoxyacetophenone **4k** (90 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 8 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.70** (73.2 mg, 75%).

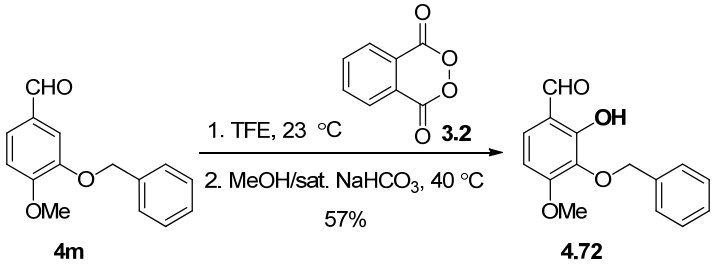
Large scale:

4.70: Prepared from general procedure B using **4k** (2.5 g, 13.8 mmol) and TFE (50 mL) at 23 °C. After 24 hours, followed the workup procedure, TFE (41 mL) was recovered. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.70** (2.04 g, 74%) as yellow solid.

4.70: m.p.: 67.0-68.5 °C, TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.6 p.p.m. (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.57 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 203.1, 158.5, 157.0, 136.4, 127.0, 115.3, 102.8, 60.6, 56.1, 26.4; IR (KBr): 2937, 1718 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0812.

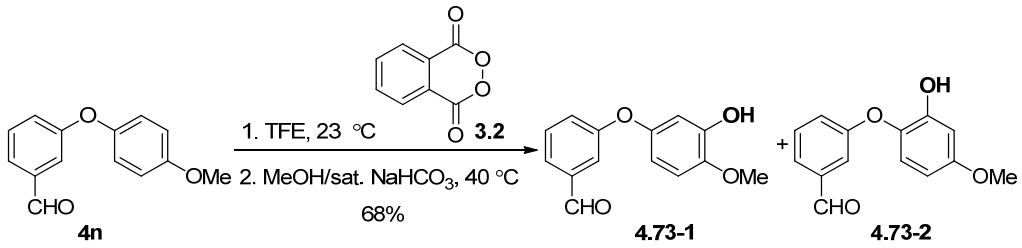


4.71: Prepared from general procedure A using 3,5-dimethoxybenzaldehyde **4l** (50 mg, 0.30 mmol) and TFE (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4l** (17.9 mg, 36%) and **4.71** (26.2 mg, 48%). The spectrums match the commercial sources.



4.72: Prepared from general procedure A using 3-benzyloxy-4-methoxybenzaldehyde **4m** (120 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4m** and **4.50** (100.5 mg, **4m** : **4.72**= 1:2.6). For characterization, the mixed compounds were dissolved in Et_2O (15 mL), which was extracted with aqueous NaOH solution (1.5 M, 3 × 5 mL), the combined aqueous layer was neutralized with aqueous HCl solution (1 M) to pH 7. Then the aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layer was washed with brine (15 mL) and dried on over Na_2SO_4. Filtered and concentrated the mixtures, **4.72** (72.6 mg, 57%) was pure enough for analysis.

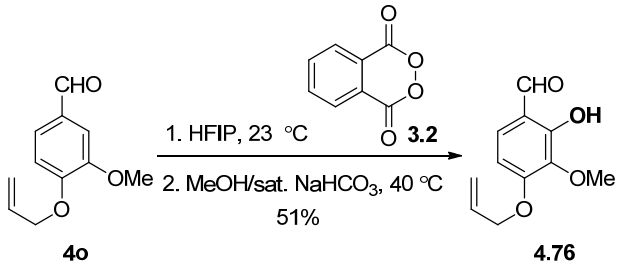
4.72: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.40; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.2 p.p.m. (s, 1H), 9.74 (s, 1H), 7.51-7.49 (m, 1H), 7.37-7.26 (s, 5H), 6.58 (d, J = 8.8 Hz, 1H), 5.09 (s, 2H), 3.90 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 194.9, 159.6, 156.0, 137.3, 134.9, 130.3, 128.5, 128.2, 128.0, 116.5, 130.9, 74.8, 56.2; IR (KBr): 3401, 1701, 1641, 1291 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_4$, 283.07843; found, 283.07841.



4.73-1 and **4.73-2**: Prepared from general procedure A using **4n** (110 mg, 0.48 mmol) and TFE (3 mL) at 23 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 2/1 hexanes/EtOAc, v/v) to afford **4n** (11.9 mg, 11%) and the mixed products (89.7 mg, 76%, **4.73-1** : **4.73-2** =1:1.4). And the resulting phenolic products **4.73-1** and **4.73-2** (20 mg) was further purified by preparative HPLC (10-90% MeCN in H_2O, 0.1% TFA, 25 minute ramp, 1mL/min, 30 mm diameter column) to afford **4.73-1** and **4.73-2** (17.9 mg, 90%) as pure material for analysis purpose. And the final yield is 68%.

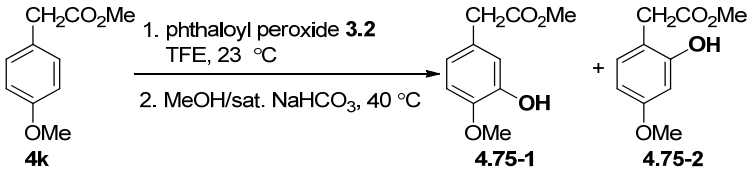
4.73-1 : 4.73-2 = 1: 1.4: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.95 p.p.m. (s, 1H), 9.94 (s, 1.4 H (1HB))*, 7.62-7.54 (m, 2.8 H (1H + 1HB)), 7.51-7.45 (m, 2.4 H (1H + 1HB)), 7.42 (dd, J = 1.2 and 2.4 Hz, 1.4 H (1HB)), 7.40 (dd, J = 1.2 and 2.4 Hz, 1H), 7.28-7.24 (m, 9.6 H (2H+2HB)), 6.89 (d, J = 9.2 Hz, 1.4 H (1HB)), 6.83 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1.4 H (1HB)), 6.55 (dd, J = 3.2 and 8.8 Hz, 1H), 6.46 (dd, J = 3.6 and 8.8 Hz, 1.4 H (1HB)), 5.73 (s, 1H), 5.42 (s, 1.4 H (1HB)), 3.91 (s,

3H), 3.81 (s, 4.2 H (3HB)); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 191.9, 191.7, 159.1, 158.7, 157.6, 149.8, 148.7, 146.6, 143.6, 137.9, 137.8, 135.6, 130.4, 130.2, 124.6, 124.3, 123.8, 122.7, 121.2, 117.1, 116.1, 111.3, 111.0, 107.3, 106.3, 102.5, 56.3, 55.7; IR (KBr): 3419, 2839, 1699, 1695, 1504, 1233 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{13}O_4$, 245.0813; found, 245.0813.
*1.4 H = one proton (1HB) for **4.73-2**



4.76: Prepared from general procedure A using 4-(allyloxy)-3-methoxybenzaldehyde **4o** (90 mg, 0.47 mmol) and HFIP (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4o** and **4.76** (66.1 mg, **4o** : **4.76**=16% : 51%). For characterization, the mixed compounds were dissolved in Et_2O (15 mL), which was extracted with aq. NaOH (1.5 M, 3 × 5 mL), the combined aqueous layer was neutralized with aq. HCl (1 M) to pH 7. Then the aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Filtered and concentrated the mixtures, **4.76** was pure enough for analysis.

4.76: TLC (pentane/Et_2O, 2/1 v/v): RF = 0.59; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.20 p.p.m. (s, 1H), 9.75 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.11-6.01 (m, 1H), 5.43 (dq, *J* = 1.6 and 17.2 Hz, 1H), 5.33 (dq, *J* = 1.6 and 17.2 Hz, 1H), 4.70 (dt, J = 1.6 and 5.2 Hz, 2H), 3.91 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 194.8, 158.4, 155.9, 136.4, 132.1, 130.0, 118.3, 116.5, 105.3, 69.6, 60.9; IR (KBr): 3421, 1647, 1501 cm^{-1}; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{12}O_4$, 208.0736; found, 208.0735.

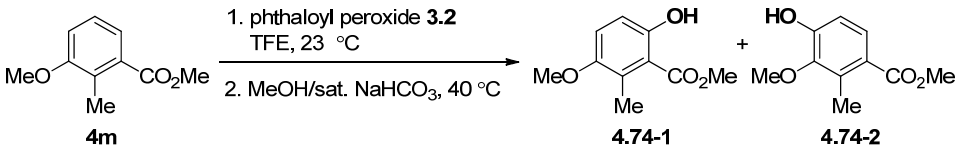


4.75-1 and **4.75-2**: Prepared from general procedure A using methyl 4-methoxyphenylacetate **4k** (90 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 8 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1

hexanes/EtOAc, v/v) to afford **4k** (13.9mg, 15%), **4.75-1**, **4.75-2** (50.0 mg, 51%, **4.75-1** : **4.75-2** = 3:1). And the resulting residue was further purified by preparative HPLC (10-90% MeCN in H_2O, 0.1% TFA, 25 minute ramp, 1mL/min, 30 mm diameter column) to afford two titled compounds as pure material for analysis.

4.75-1: TLC (hexanes/EtOAc, 4/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.86 p.p.m. (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.74 (dd, J = 2.0 and 8.4 Hz, 1H), 5.59 (s, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.53 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2, 145.7, 145.6, 127.1, 120.8, 115.5, 110.6, 55.9, 52.0, 40.6; IR (KBr): 3343, 1725 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{12}NaO_4$, 219.06278; found, 219.06254.

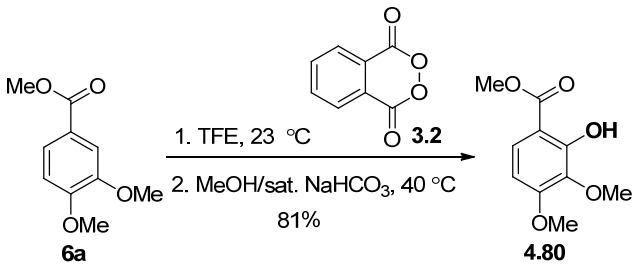
4.75-2: TLC (hexanes/EtOAc, 4/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 p.p.m. (brs, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 2.8 Hz, 1H), 6.44 (dd, J = 2.8 and 8.4 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.62 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 174.8, 160.7, 156.3, 131.4, 112.6, 106.8, 103.5, 52.7, 37.2, 27.2; IR (KBr): 3390, 1719, 1621 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{12}NaO_4$, 219.06278; found, 219.06283.



4.74-1 and **4.74-2**: Prepared from general procedure A using methyl 3-methoxy-2-methylbenzoate **4m** (80 mg, 0.45 mmol) and TFE (3 mL) at 23 °C. After 6 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 2/1 pentane/Et_2O, v/v) to afford **4m** (17.1 mg, 19%), **4.74-1** (33.2 mg, 34%) and **4.74-2** (17.5 mg, 18%).

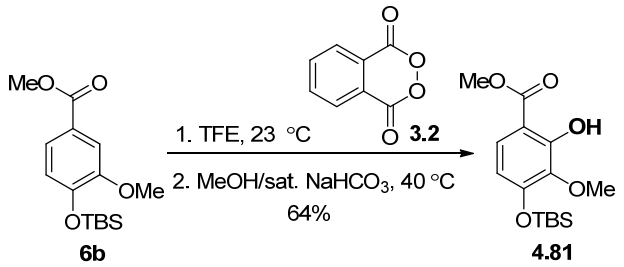
4.74-1: m.p.: 62.5-64.0 °C, TLC (pentane/Et_2O, 10/1 v/v): RF = 0.65; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.4 p.p.m. (s, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.82 (dd, J = 0.8 and 9.2 Hz, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.8, 155.8, 150.8, 129.1, 119.3, 114.9, 113.7, 57.1, 52.2, 14.4; IR (KBr): 3368, 1718, 1384 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0814.

4.74-2: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.45; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 p.p.m. (d, J = 8.4 Hz, 1H), 6.83 (dd, J = 0.8 and 8.4 Hz, 1H), 6.04 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 2.55 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 152.2, 145.7, 134.3, 128.2, 122.5, 112.4, 61.0, 51.6, 13.7; IR (KBr): 3393, 1716, 1057 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0814.



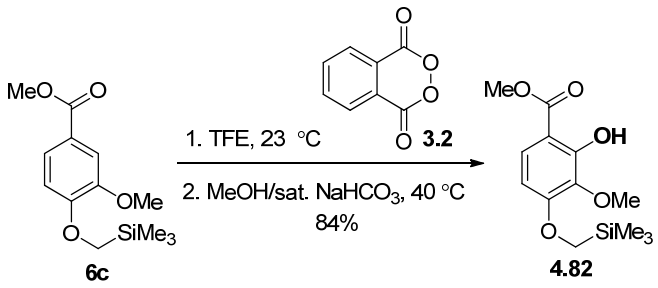
4.80: Prepared from general procedure A using methyl 3-methoxy-2-methylbenzoate **6a** (100 mg, 0.51 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.80** (87.9 mg, 81%).

4.80: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.90 p.p.m. (s, 1H), 7.59 (d, J = 9.2 Hz, 1H), 6.48 (d, J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 158.0, 155.9, 136.5, 125.7, 107.0, 103.1, 60.7, 56.0, 52.1; IR (KBr): 2954, 1679, 1088 cm^{-1}; HRMS (m/z): $[M+Na]^+$ calcd for $C_{10}H_{12}NaO_5$, 235.05769; found, 235.05775.

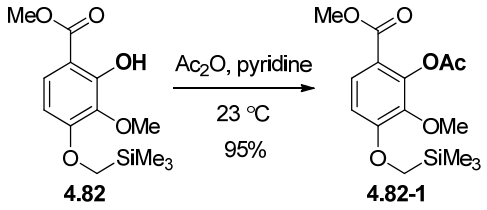


4.81: Prepared from general procedure A using **6b** (100 mg, 0.34 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.81** (67.0 mg, 64%).

4.81: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.79; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.95 p.p.m. (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 6.39 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 156.9, 154.9, 139.2, 125.0, 112.5, 107.3, 60.2, 52.1, 25.6, 18.3, -4.6; IR (KBr): 2955, 2931, 1674 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{15}H_{25}O_5Si$, 313.1471; found, 313.1471.

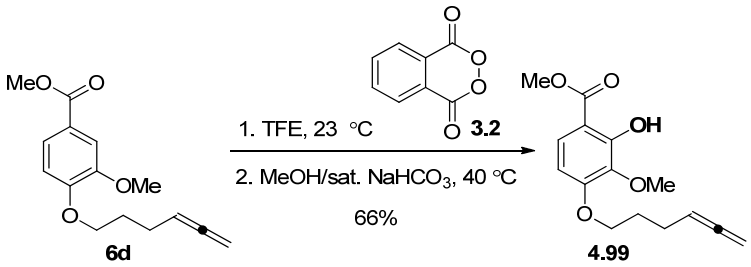


4.82: Prepared from general procedure A using **6c** (100 mg, 0.37 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.82** (88.9 mg, 84%).



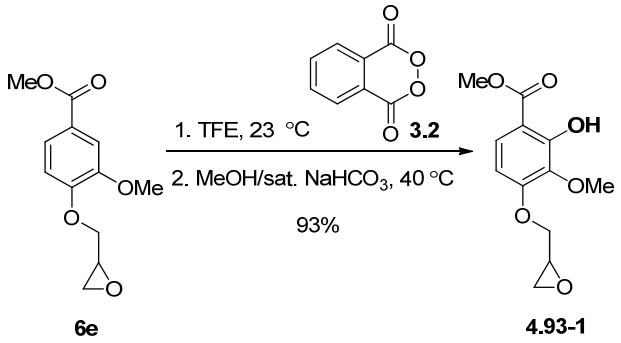
4.82-1: To compound **4.82** (88.9 mg, 0.31 mmol), pyridine (0.8 mL) and acetic anhydride (1 mL) were added. The reaction mixture was stirred for 18 hours. The volatile was removed under reduced pressure. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4.82-1** (97.1 mg, 95%). The total yield in two steps is 80%,

4.82-1: TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 p.p.m. (d, J = 8.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.66 (s, 2H), 2.38 (s, 3H), 0.17 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.3, 164.7, 159.2, 144.9, 141.7, 127.0, 115.6, 109.1, 62.1, 60.8, 51.9, 20.7, -3.1; IR (KBr): 2954, 1769, 1720 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{22}O_6Si$, 326.1186; found, 326.1187.

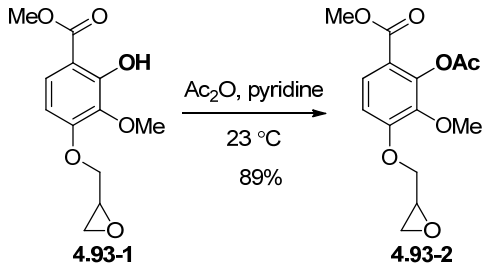


4.99: Prepared from general procedure A using **6d** (130 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.99** (91.2 mg, 66%).

4.99: TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.88 p.p.m. (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 5.19-5.12 (m, 1H), 4.69 (penta, J = 3.2 Hz, 2H), 4.10 (t, J = 6.8 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.25-2.18 (m, 2H), 1.97 (penta, J = 6.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.6, 170.4, 157.6, 156.0, 136.7, 125.5, 106.8, 104.2, 89.0, 75.4, 68.0, 60.7, 52.1, 28.3, 24.5; IR (KBr): 2953, 1955, 1673, 1507 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{19}O_5$, 279.1232; found, 279.1231.

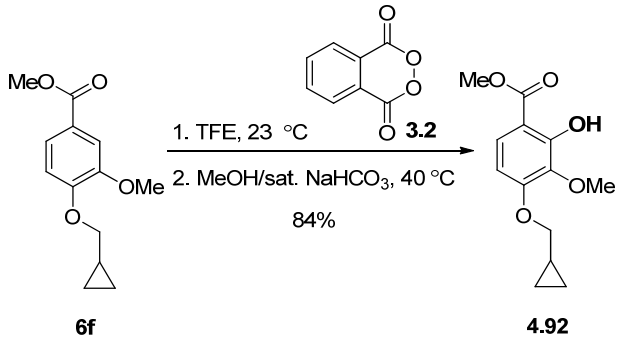


4.93-1: Prepared from general procedure A using **6e** (110 mg, 0.46 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 2/1 hexanes/EtOAc, v/v) to afford **4.93-1** (108.9 mg, 93%).



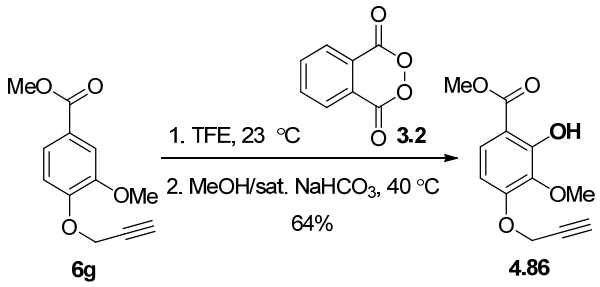
4.93-2: To **4.93-1** (110 mg, 0.43 mmol), pyridine (0.8 mL) and acetic anhydride (1 mL) were added. The reaction mixture was stirred overnight. The volatile was removed under reduced pressure. The reaction crude mixture was purified by silica gel column chromatography (15/1 → 4/1 hexanes/EtOAc, v/v) to afford **4.93-2** (119 mg, 93%). The total yield in two steps is 89%.

4.69-2: TLC (hexanes/EtOAc, 2/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 p.p.m. (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.35 (dd, J = 3.2 and 11.2 Hz, 1H), 4.03 (ddd, J = 0.4, 5.6 and 11.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.41-3.37 (m, 1H), 2.92 (dt, J = 0.4 and 4.4 Hz, 1H), 2.78 (ddd, J = 0.4, 2.8 and 4.4 Hz, 1H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.2, 164.5, 156.1, 145.3, 142.1, 127.0, 116.9, 110.3, 69.7, 61.0, 52.0, 49.8, 44.5, 20.7; IR (KBr): 3433, 2951, 1769, 1720, 12.8 cm^{-1}; HRMS (m/z): $[M+Na]^+$ calcd for $C_{14}H_{16}NaO_7$, 319.07882; found, 319.07918.



4.92: Prepared from general procedure A using **6f** (100 mg, 0.42 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.92** (90.1 mg, 84%).

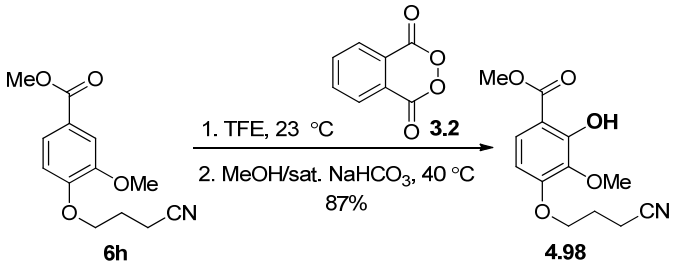
4.92: m.p.: 58.5-59.5 °C, TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.65; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.89 p.p.m. (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 3.92-3.90 (m, 8H), 1.35-1.26 (m, 1H), 0.67-0.62 (m, 2H), 0.38-0.35 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 157.6, 156.0, 136.8, 125.5, 106.8, 104.5, 73.6, 60.6, 52.1, 10.2, 3.3; IR (KBr): 3084, 3003, 1672, 1284 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{16}O_5$, 252.0998; found, 252.0999.



4.86: Prepared from general procedure A using **6g** (100 mg, 0.45 mmol) and TFE (2.5 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by

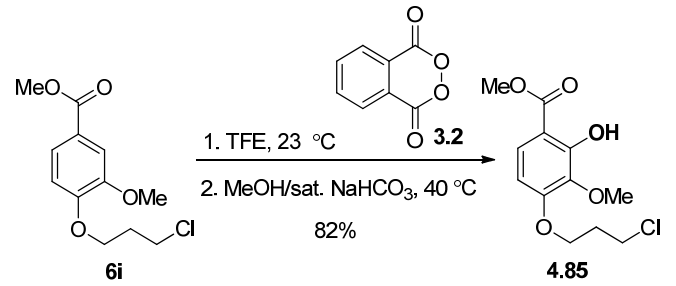
silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.62** (68.9 mg, 64%).

4.86: m.p.: 99.9-101.4 °C, TLC (hexanes/EtOAc, 2/1 v/v): RF = 0.75; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.92 p.p.m. (s, 1H), 7.58 (d, J = 9.2 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 4.80 (d, J = 2.4 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.53 (t, J = 2.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 156.1, 157.8, 137.6, 125.8, 107.9, 105.0, 77.9, 76.2, 60.7, 56.5, 52.1; IR (KBr): 3266, 1677 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{12}O_5$, 236.0685; found, 236.0682.



4.98: Prepared from general procedure A using **6h** (120 mg, 0.48 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 2/1 hexanes/EtOAc, v/v) to afford **4.98** (110.8 mg, 87%).

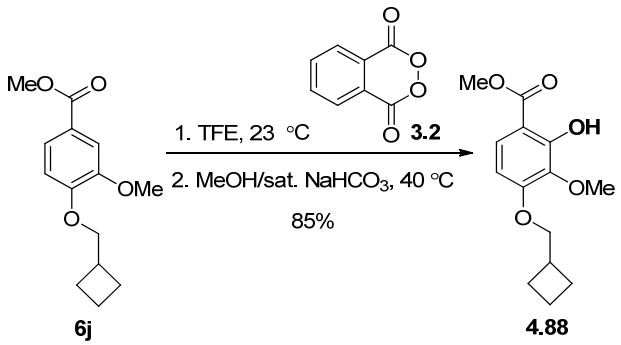
4.98: TLC (hexanes/EtOAc, 2/1 v/v): RF = 0.40; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.93 p.p.m. (s, 1H), 7.58 (d, J = 9.2 Hz, 1H), 6.46 (d, J = 9.2 Hz, 1H), 4.19 (t, J = 5.6 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 2.64 (t, J = 5.6 Hz, 2H), 2.20 (penta, J = 5.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 156.8, 156.2, 136.9, 125.7, 118.9, 107.6, 104.4, 66.3, 60.8, 52.2, 25.4, 10.1; IR (KBr): 2955, 1718, 1674, 1439 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{16}NO_5$, 266.10230; found, 266.10243.



4.85: Prepared from general procedure A using **6i** (120 mg, 0.46 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by

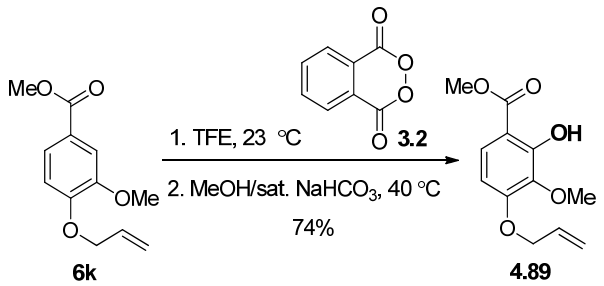
silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.85** (104.1 mg, 82%).

4.85: m.p.: 99.9-101.4 °C, TLC (hexanes/EtOAc, 4/1 v/v): RF = 0.75; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.91 p.p.m. (s, 1H), 7.57 (d, J = 9.2 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 4.21 (t, J = 5.6 Hz, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.79 (t, J = 5.6 Hz, 2H), 2.29 (penta, J = 5.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 157.2, 156.1, 136.7, 125.7, 107.1, 104.2, 65.2, 60.7, 52.2, 41.3, 32.0; IR (KBr): 3140, 2955, 1674, 1286 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{15}O_5{}^{35}Cl$, 274.0608; found, 274.0610.



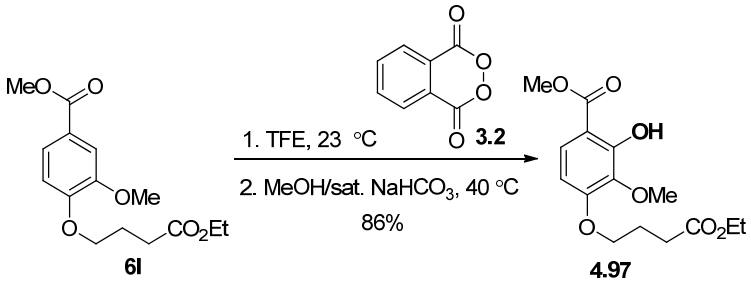
4.88: Prepared from general procedure A using **6j** (100 mg, 0.40 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.88** (90.5 mg, 85%).

4.88: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.87 p.p.m. (s, 1H), 7.55 (d, J = 9.2 Hz, 1H), 6.45 (d, J = 9.2 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.88-2.80 (m, 1H), 2.20-2.10 (m, 2H), 2.04-1.83 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 157.9, 156.0, 136.7, 125.5, 106.7, 104.3, 72.8, 60.6, 52.1, 34.4, 24.8, 18.5; IR (KBr): 2937, 1673 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}O_5$, 267.1232; found, 267.1229.



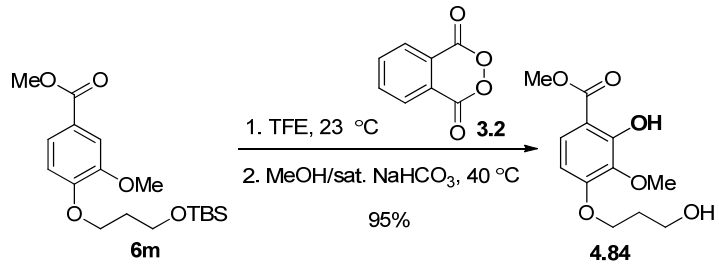
4.89: Prepared from general procedure A using **6k** (110 mg, 0.50 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.89** (87.5 mg, 74%).

4.89: m.p.: 56.5-57.9 °C, TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.90 p.p.m. (s, 1H), 7.53 (d, J = 9.2 Hz, 1H), 6.45 (d, J = 9.2 Hz, 1H), 6.09-5.99 (m, 1H), 5.43-5.38 (m, 1H), 5.31-5.27 (m, 1H), 4.65-4.63 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 157.0, 156.0, 136.7, 132.5, 125.4, 117.9, 106.9, 104.5, 69.4, 60.6, 52.1; IR (KBr): 3019, 1670, 1384 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{12}O_5$, 238.0841; found, 238.0841.



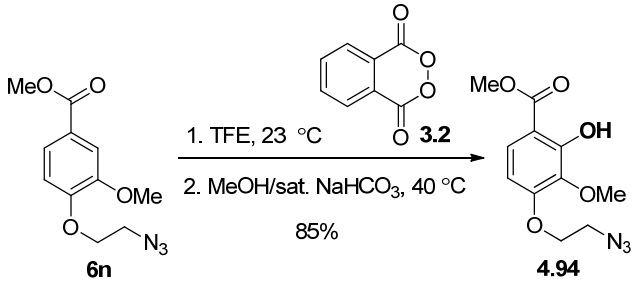
4.97: Prepared from general procedure A using **6l** (140 mg, 0.47 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.97** (126.6 mg, 86%).

4.97: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.89 p.p.m. (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 4.17-4.08 (m, 4H), 3.91 (s, 3H), 3.88 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.16 (dpenta, J = 0.8 and 7.2 Hz, 2H), 2.51 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0, 170.4, 157.4, 156.1, 136.7, 125.6, 107.0, 104.2, 67.7, 60.7, 60.5, 52.1, 30.6, 24.5, 14.2; IR (KBr): 3139, 2956, 1733, 1674, 1285 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}NaO_7$, 335.11012; found, 335.11035.



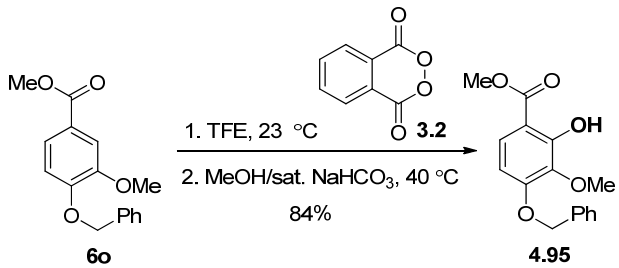
4.84: Prepared from general procedure A using **6m** (160 mg, 0.45 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 1/1 hexanes/EtOAc, v/v) to afford **4.84** (110.1 mg, 95%). From the crude NMR, no silyl group was deprotected. After column chromatography, the TBS group was deprotected cleanly on silica gel.

4.84: TLC (hexanes/EtOAc, 1/1 v/v): RF = 0.42; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.90 p.p.m. (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.23-4.18 (m, 2H), 3.91-3.84 (m, 8H), 2.11-2.03 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 157.3, 156.0, 136.6, 125.7, 107.1, 104.1, 67.0, 60.6, 60.3, 52.1, 31.8; IR (KBr): 3391, 1673 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{16}O_6$, 256.0947; found, 256.0945.



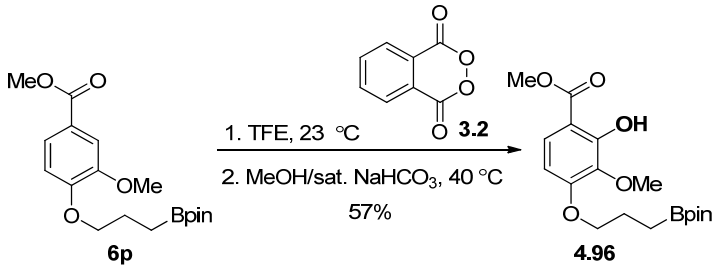
4.94: Prepared from general procedure A using **6n** (150 mg, 0.60 mmol) and TFE (4 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.94** (135.5 mg, 85%).

4.94: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.93 p.p.m. (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 4.23 (t, J = 4.8 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.66 (t, J = 4.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 156.7, 156.3, 137.1, 125.6, 107.7, 104.5, 67.9, 60.8, 52.2, 50.2; IR (KBr): 2955, 2108, 1673, 1289 cm^{-1}; HRMS (m/z): $[M+H]^+$ calcd for $C_{11}H_{14}N_3O_5$, 268.0933; found, 268.0935.



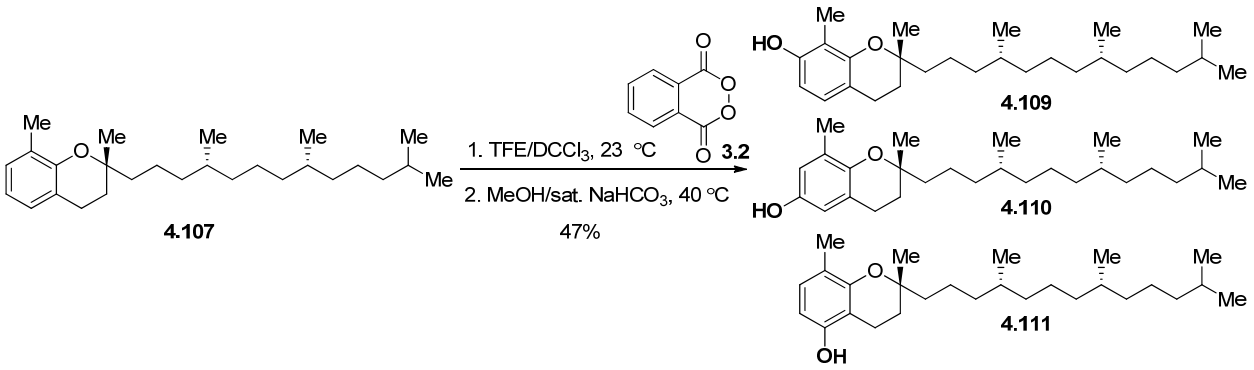
4.95: Prepared from general procedure A using **6o** (95 mg, 0.35 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford **4.95** (84.1 mg, 84%).

4.95: m.p.: 63.0-64.5 °C, TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.60; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.91 p.p.m. (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.43-7.24 (m, 5H), 6.48 (d, J = 8.8 Hz, 1H), 5.18 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.66 (t, J = 4.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 157.1, 156.1, 137.1, 136.3, 128.6, 128.0, 127.1, 125.5, 107.1, 104.9, 70.6, 60.7, 52.1; IR (KBr): 3030, 1673, 1618 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{16}H_{16}O_5$, 288.0998; found, 288.0998.



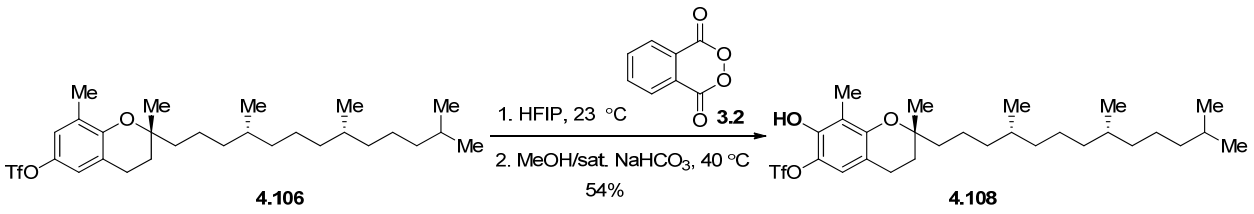
4.96: Prepared from general procedure A using **6p** (80 mg, 0.23 mmol) and TFE (3 mL) at 23 °C. After 3 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 5/1 hexanes/EtOAc, v/v) to afford **4.96** (47.9 mg, 57%).

4.96: TLC (hexanes/EtOAc, 5/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.87 p.p.m. (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.05 (t, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 1.95 (penta, J = 6.8 Hz, 2H), 1.24 (s, 12H), 0.93 (t, J = 6.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 157.7, 156.0, 136.7, 125.5, 106.6, 104.3, 83.2, 70.5, 60.7, 52.1, 24.8, 23.6; IR (KBr): 2978, 1673, 1439 cm^{-1}; HRMS (m/z): $[M]^+$ calcd for $C_{18}H_{27}{}^{11}BO_7$, 367.1928; found, 367.1935.



4.109, 4.110 and 4.111: Prepared from general procedure A using **4.107** (100 mg, 0.26 mmol), TFE (2 mL) and $DCCl_3$ (4 mL) at 23 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 1/3 hexanes/CH_2Cl_2, v/v) to afford **4.107** (25.5 mg, 26%), tocopherol **4.110** (19.9 mg, 19%), **4.109** and **4.111** (29.1 mg, 28%, **4.109** : **4.111** = 1.5:1) as yellow oil. The spectrums of tocopherol **4.110** match the commercial sources.

4.109 : 4.111 = 1.5:1: TLC (hexanes/CH_2Cl_2, 1:3 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.81 p.p.m. (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1.5 H' (1HA))*, 6.32 (d, J = 8.0 Hz, 1.5 H' (HA)), 6.24 (d, J = 8.0 Hz, 1H), 4.55 (s, 1H), 4.54 (s, 1.5 H' (HA)), 2.70-2.62 (m, 2H+3H'(2HA)), 2.09 (s, 3H), 2.97 (s, 4.5 H' (3HA)), 2.05-1.58 (m, 2H+3H'(2HA)), 1.58-1.03 (m, 24H + 36 H' (24HA)), 1.01-1.83 (m, 12H + 18H' (12 HA)); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.6, 152.5, 151.7, 127.6, 126.4, 118.4, 113.2, 111.4, 108.0, 106.4, 104.8, 76.1, 75.6, 40.1, 39.8, 39.4, 37.4, 37.3, 32.8, 32.7, 31.2, 30.4, 28.0, 24.8, 24.4, 24.2, 24.0, 22.7, 22.6, 21.8, 21.0, 20.9, 19.7, 19.6, 16.8, 15.5, 7.9; IR (KBr): 3431, 2925, 1612, 1462 cm^{-1}; HRMS (m/z): [M-H]$^-$ calcd for $C_{27}H_{45}O_2$, 401.34256; found, 401.34266.
*1.5 H' = one proton (1HA) for **4.109**

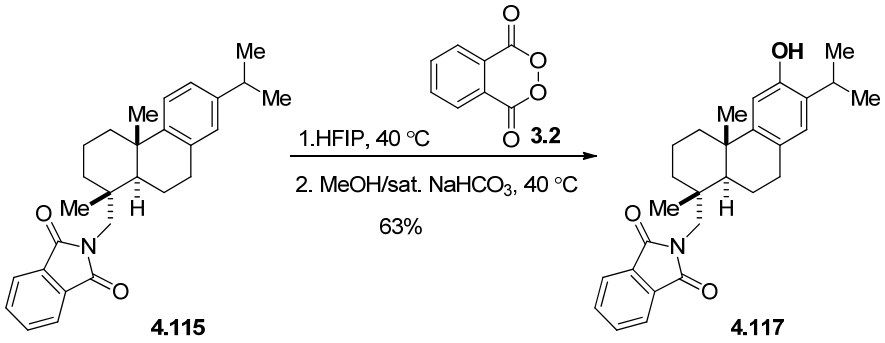


4.108: Prepared from general procedure A using **4.106** (100 mg, 0.19 mmol), HFIP (2.5 mL) at 23 °C. After 12 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (10/1 → 1/1 hexanes/CH_2Cl_2, v/v) to afford **4.106** (11.9 mg, 12%) and **4.108** (55.1 mg, 54%) as yellow oil.

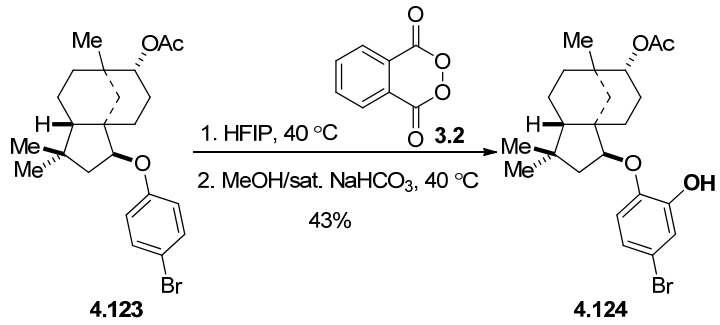
Large scale:

Prepared from general procedure B using **4.106** (12 g, 22.4 mmol) and HFIP (200 mL) at 23 °C for 24 hours. HFIP (190 mL) was recovered. Followed the workup procedure, the reaction crude mixture was purified by2silica gel column chromatography (10/1 → 1/1 hexanes/CH_2Cl_2, v/v) to afford **4.106** (1.7 g, 14%) and **4.108** (5.5 g, 45%) as deep yellow oil.

4.108: TLC (hexanes/CH_2Cl_2, 1/1 v/v): RF = 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.96 p.p.m. (s, 1H), 4.95 (brs, 1H), 2.72-2.58 (m, 2H), 2.09 (s, 3H), 1.82-1.69 (m, 2H), 1.64-1.05 (m, 24H), 0.90-0.81 (m, 12 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.9, 144.0, 130.5, 118.7, 118.6 (q, J = 303 Hz) 114.6, 113.5, 76.9, 40.1, 39.4, 37.43, 37.37, 37.3, 32.8, 32.7, 30.8, 28.0, 24.8, 24.4, 24.1, 22.7, 22.6, 21.8, 20.9, 19.7, 19.6, 8.5; IR (KBr): 3555, 2927, 1421, 1213 cm^{-1}; HRMS (m/z): $[M+Na]^+$ calcd for $C_{28}H_{45}F_3NaO_5S$, 573.28320; found, 573.28307.



4.117: Prepared from general procedure A using **4.115** (141 mg, 0.34 mmol), HFIP (3 mL) at 40 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 1/1 hexanes/EtOAc, v/v) to afford the **4.117** (10.1 mg, 7%) and **13** (92.5 mg, 63%) as pale yellow oil. The spectrum data matched the literature data[7].

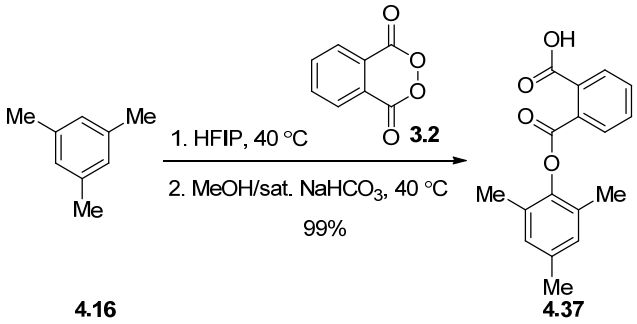


4.124: Prepared from general procedure A using **4.123** (850 mg, 1.96 mmol), HFIP (10 mL) at 23 °C. After 24 hours, followed the workup procedure, the reaction crude mixture was purified by silica gel column chromatography (15/1 → 10/1 hexanes/EtOAc, v/v) to afford the **4.123** (315 mg, 37%) and **4.124** (400 mg, 43%) as pale yellow oil.

4.124: TLC (hexanes/EtOAc, 10/1 v/v): RF = 0.55; ^{1}H-NMR (400 MHz, C_6D_6): δ 7.07 p.p.m. (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 2.4 and 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.64 (s, 1H), 4.58 (dd, J = 1.6 and 8.0 Hz, 1H), 2.04-1.97 (m, 4H), 1.90 (dd, J = 6.4 and 8.8 Hz, 1H), 1.76-1.53 (m, 4H), 1.53-1.36 (m, 4H), 1.29-1.22 (m, 2H), 1.13 (d, J = 12.4 Hz, 1H), 1.07 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C-NMR (150 MHz, C_6D_6): δ 170.8, 147.4, 144.9, 122.7, 117.9, 114.5, 113.2, 87.8, 76.5, 50.3, 45.1, 44.2, 38.2, 37.0, 33.7, 32.7, 31.6, 28.0, 27.9, 25.5, 23.9, 21.3, 20.6; IR (KBr): 3531, 2952, 1719, 1494 cm^{-1}; HRMS (m/z): $[M+NH_4]^+$ calcd for $C_{23}H_{31}{}^{81}BrNaO_4$, 475.12807; found, 475.12797.

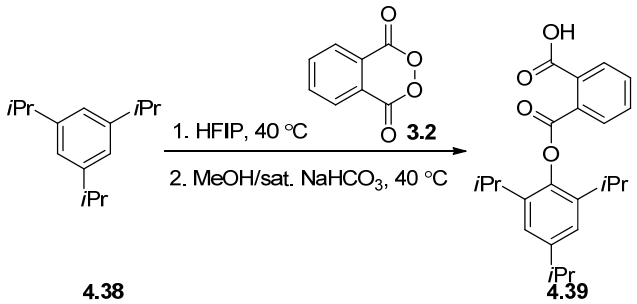
Procedure to isolate the *mono*-phthalic acid ester **4.37**, **4.39** and spectrum data:

General Procedure C: A borosilicate vial was equipped with a magnetic stir bar and corresponding arenes (1.0 mmol, 1.0 equiv.) and HFIP (5 mL, ~0.3 M) was added by syringe to make homogeneous solution. To the resulting solution, phthaloyl peroxide (1.3 equiv.) was added in small portions and the vial was sealed with a septa screw cap and placed in a 40 °C oil bath. After 24 hours, the reaction crude was cooled and the solvent was evaporated slowly by a steam of N_2 flow, at one time, some yellow brown crystalline solid was precipitated. The solid was either (i) carefully picked up by tweezers and washed with pentane and dried, or (ii) quickly purified by silica gel column chromatography (5/1 → 1/1 hexanes/EtOAc, v/v) to afford the adduct.



4.19: Prepared from general procedure C using mesitylene **4.16** (50 mg, 0.42 mmol), HFIP (2 mL). After 24 hours, followed the workup procedure (ii), the pale yellow solid **4.37** (117 mg, 99%) was isolated and the crystal was further grown in ether solution.

4.37: m.p. 140.5-142.5 °C; TLC (hexanes/EtOAc, 1/1 v/v): RF = 0.28; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 p.p.m. (m, 1H), 7.90-7.88 (m, 1H), 7.69-7.65 (m, 2H), 6.91 (s, 2H), 2.29 (s, 3H), 2.24 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.1, 165.1, 145.8, 136.0, 135.6, 131.73, 131.68, 131.4, 130.0, 129.7, 129.5, 129.4, 128.3, 125.7, 20.8, 16.4; IR (KBr): 2920, 1753, 1702, 1384cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{16}NaO_4$, 307.09463; found, 307.09476.



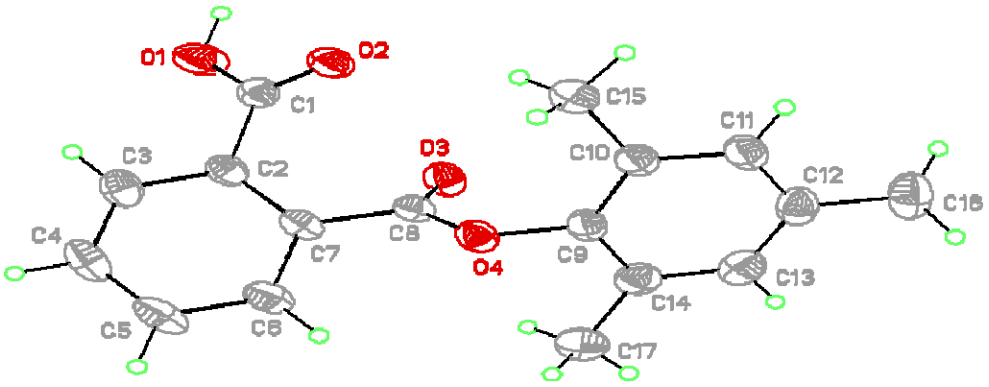
4.38 **4.39**

4.39: Prepared from general procedure C using 1,3,5-triisopropylbezene **4.38** (1.0 g, 4.9 mmol), HFIP (20 mL). After 24 hours, followed the workup procedure (i), the brown solid was good for characterization.

4.39: m.p. shrink above 130 °C ; TLC (hexanes/EtOAc, 1/1 v/v): RF = 0.25; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.15-8.12 p.p.m. (m, 1H), 7.89-7.86 (m, 1H), 7.69-7.67 (m, 2H), 7.04 (s, 2H), 3.06 (hepta, J = 6.8 Hz, 2H), 2.91 (hepta, J = 6.8 Hz, 1H), 1.26 (d, J = 7.2 Hz, 6H), 1.22 (d, J = 7.2 Hz, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.1, 165.8, 147.0, 143.3, 140.0, 132.9, 132.3, 131.5, 130.2, 129.9, 129.8, 122.0, 34.1, 27.4, 24.1; IR (KBr): 2963, 1740, 1705, 1260 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{28}NaO_4$, 391.18798; found, 391.18804.

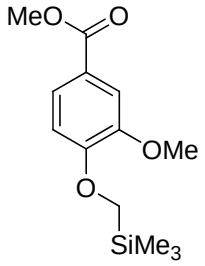
III. Crystal data

Crystal data of 4.37:



View of **4.37** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

4.8 Spectrum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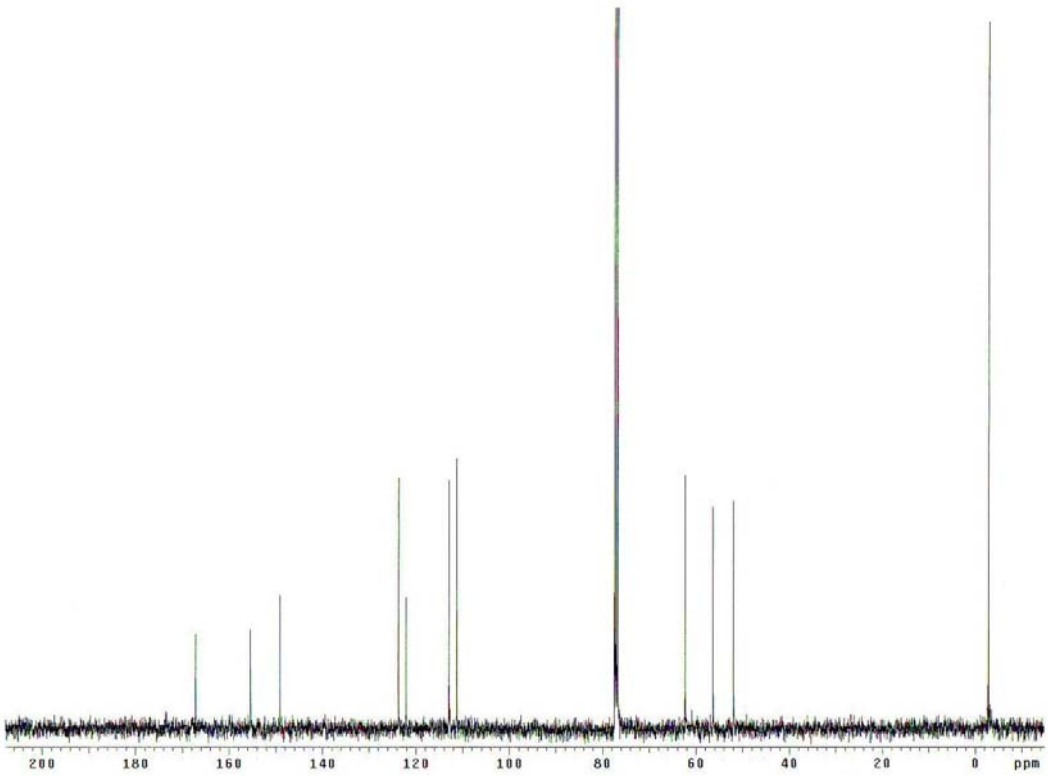
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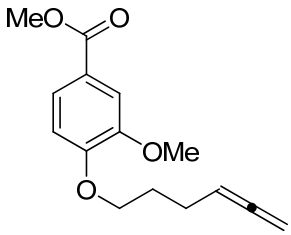
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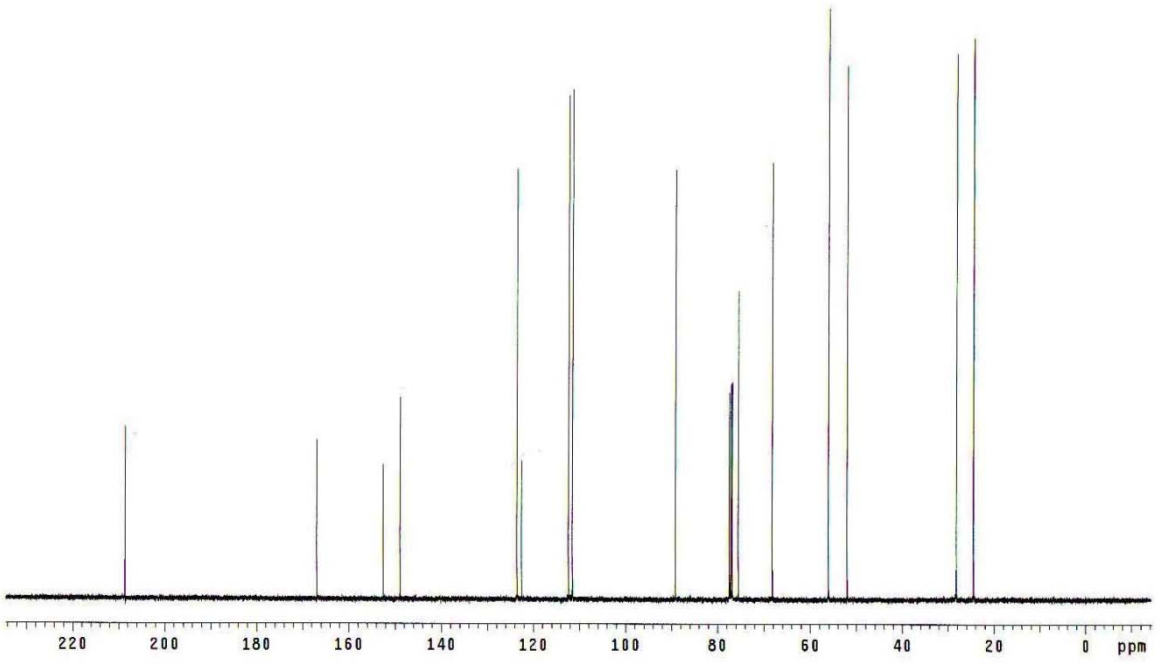
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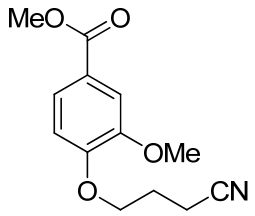
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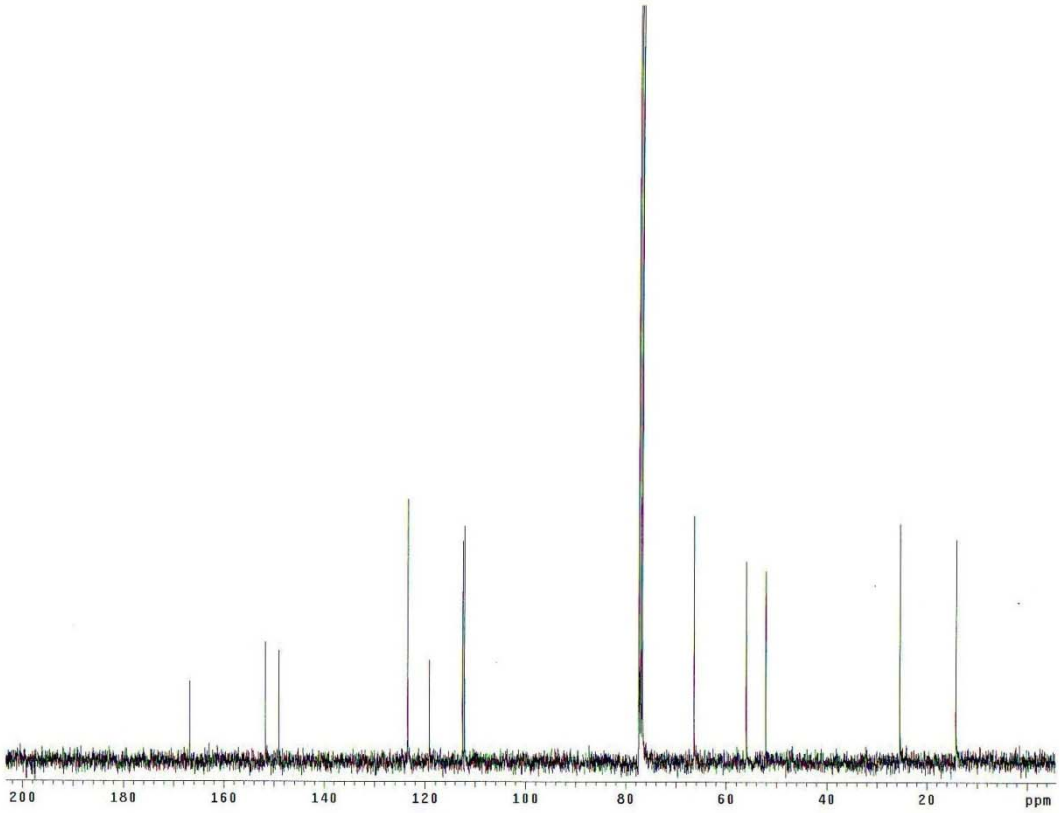
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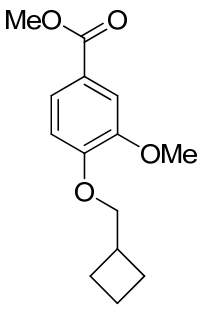
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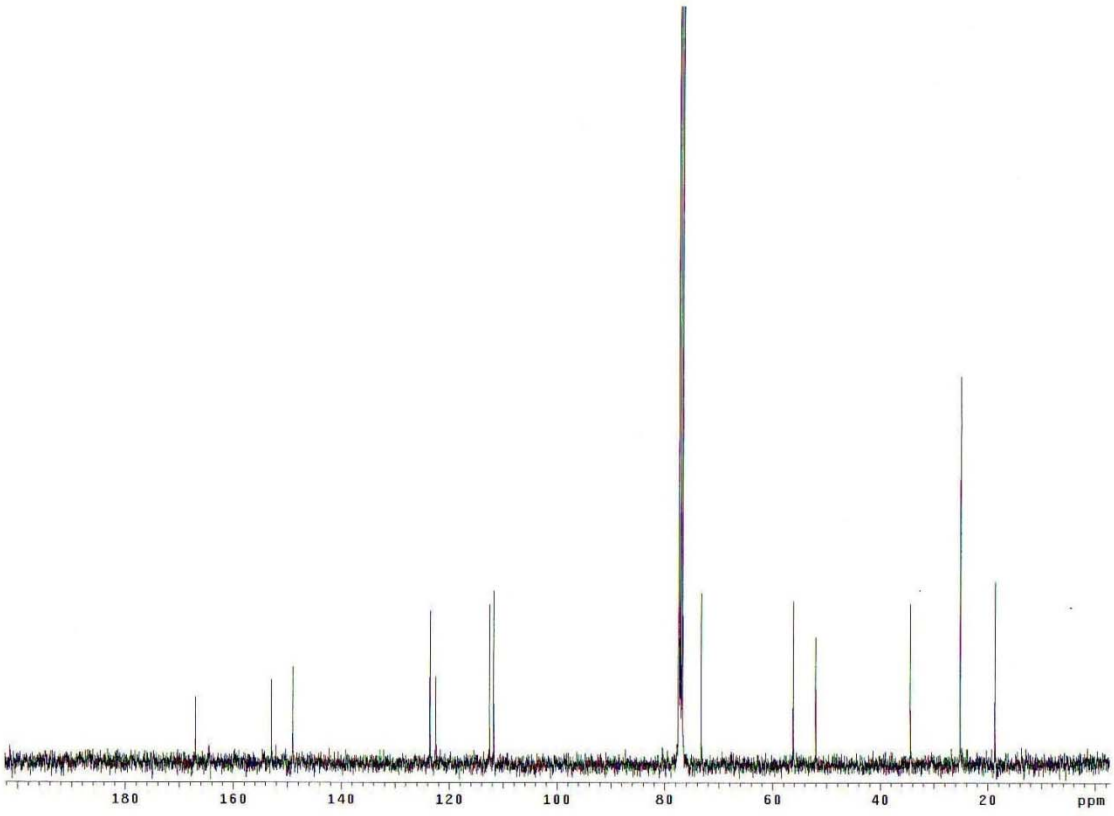
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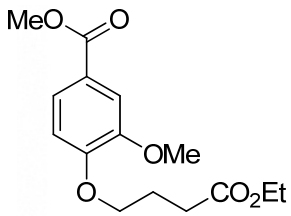
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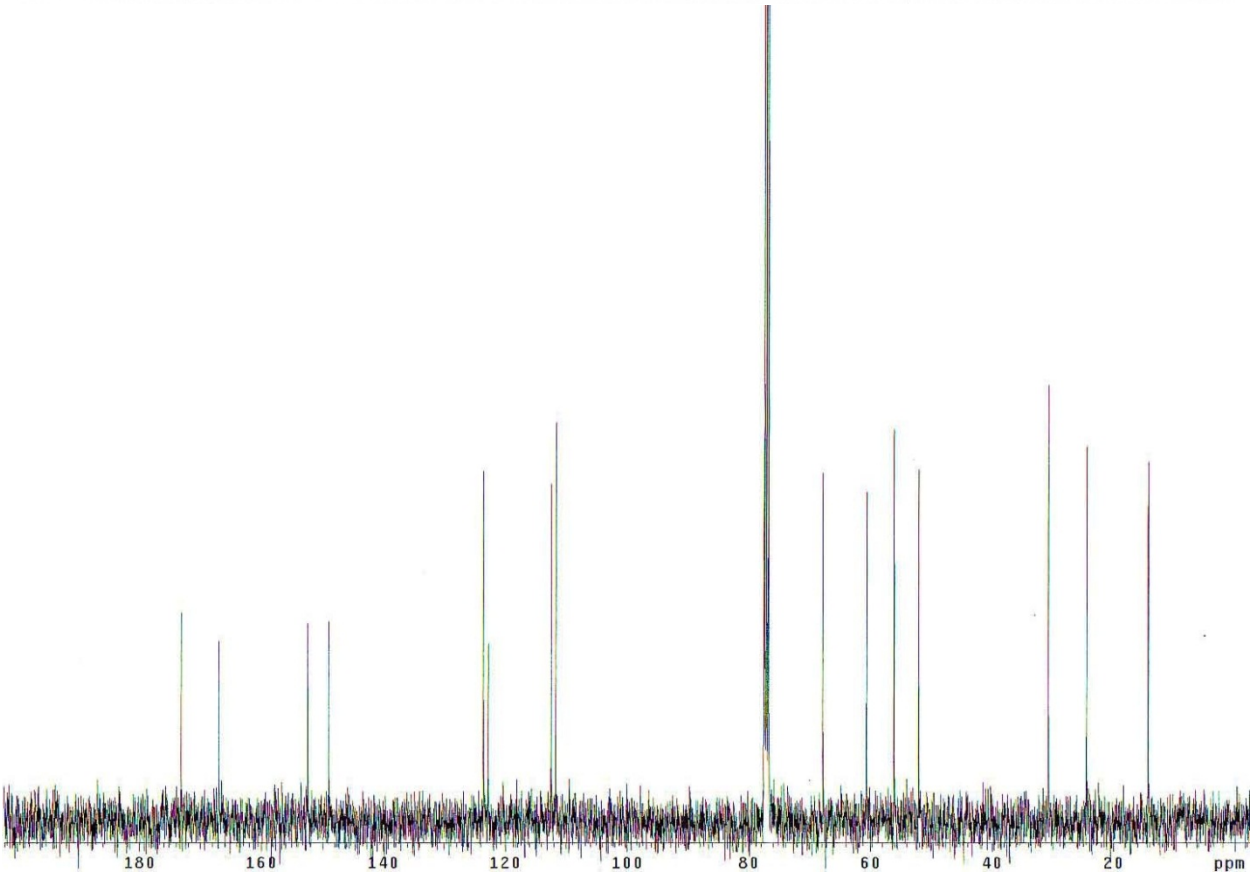
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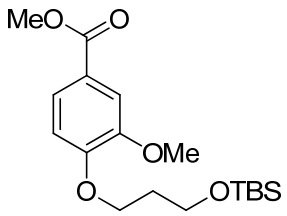
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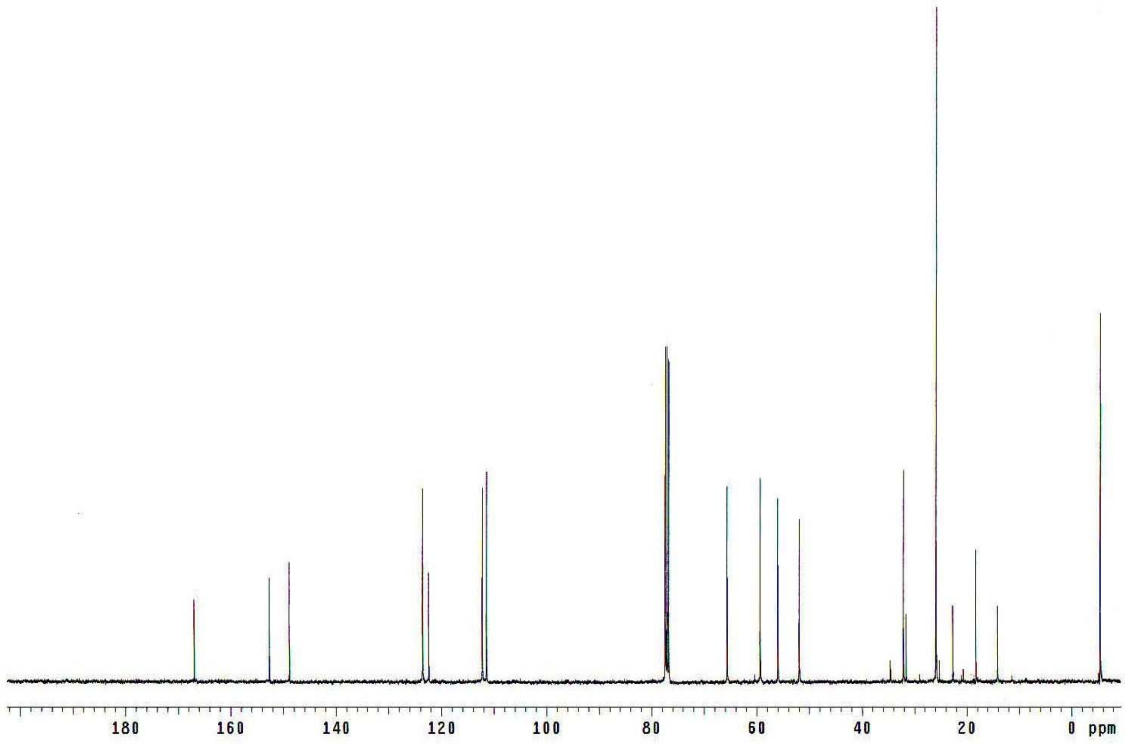
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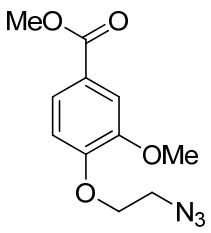
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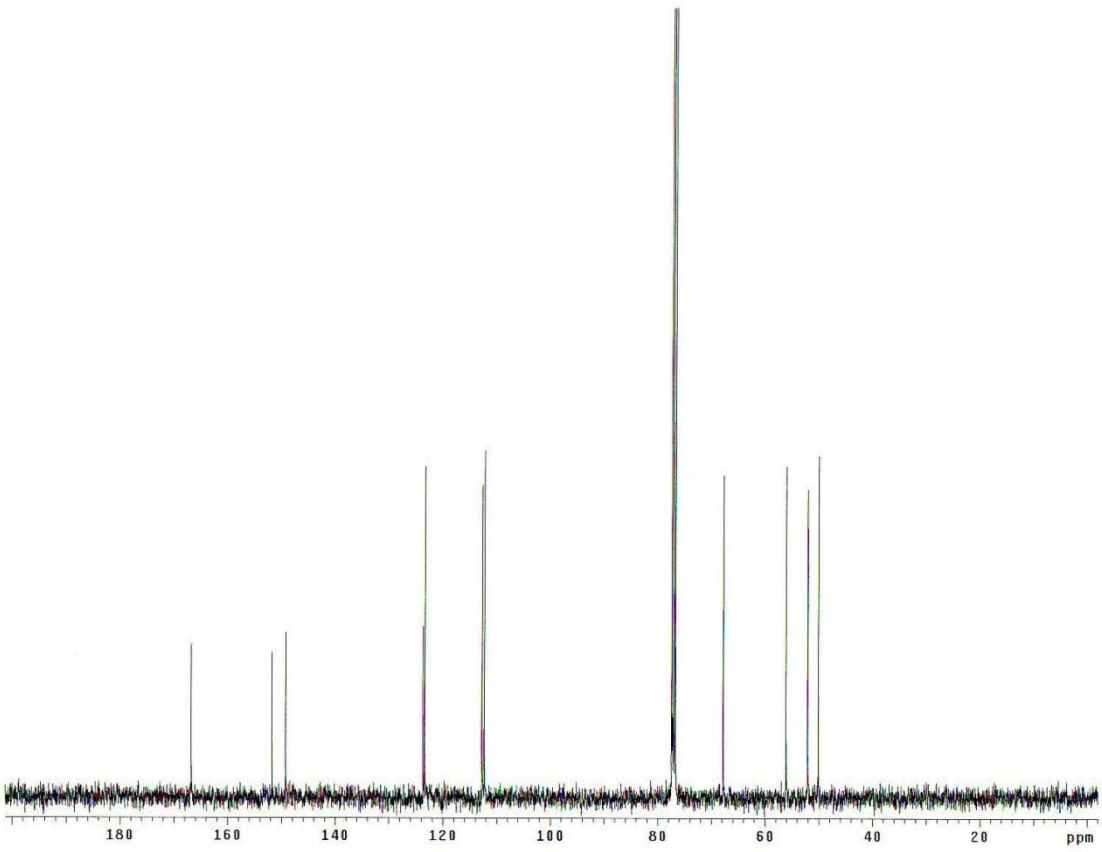
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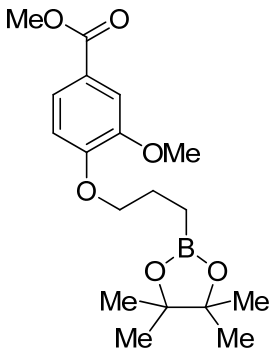
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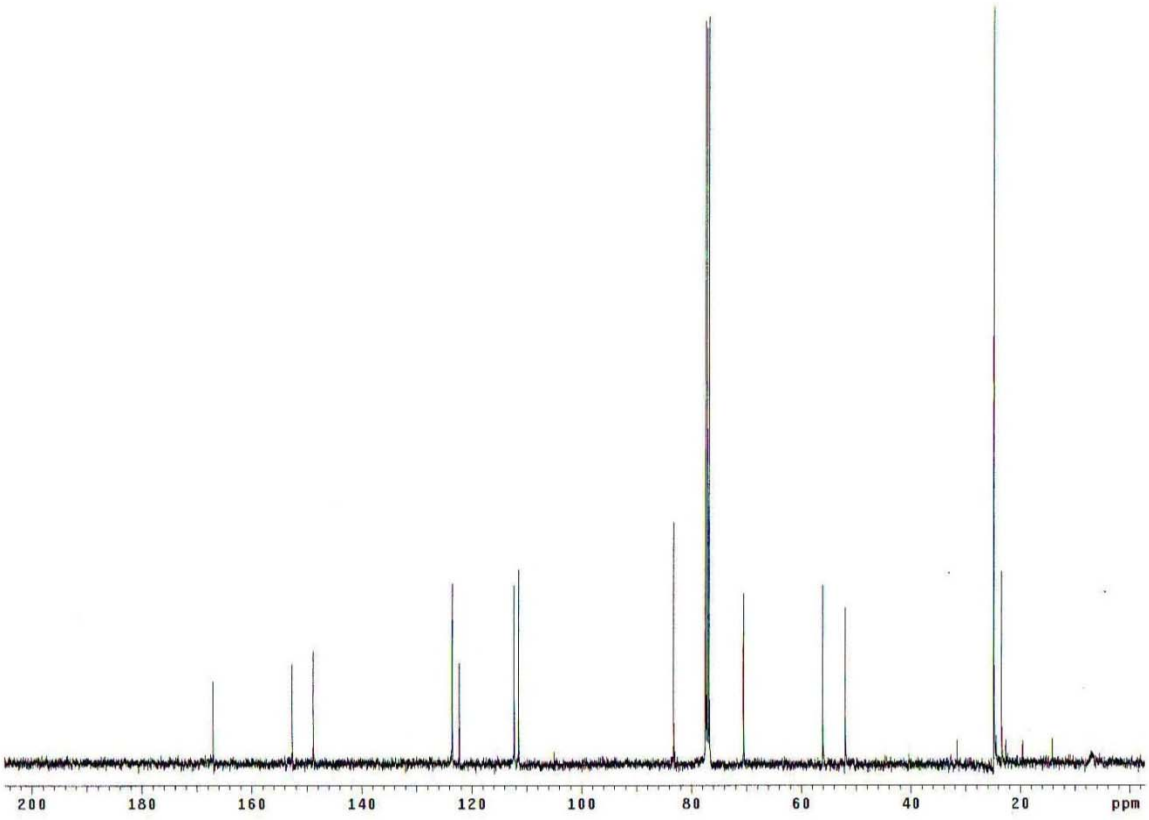
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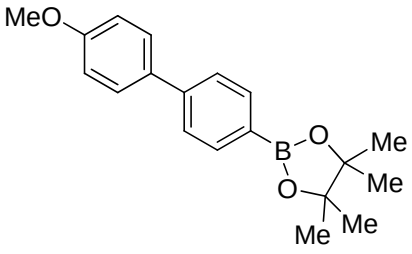
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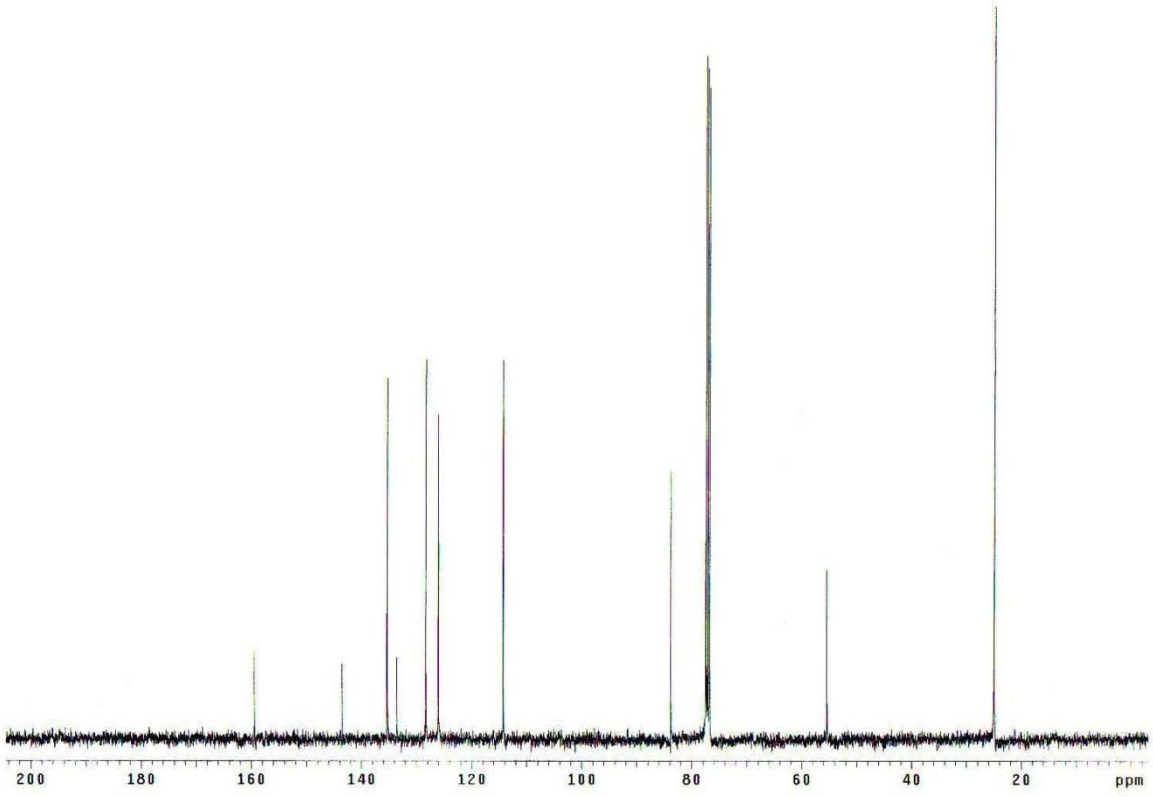
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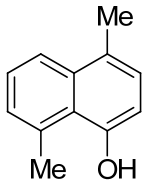
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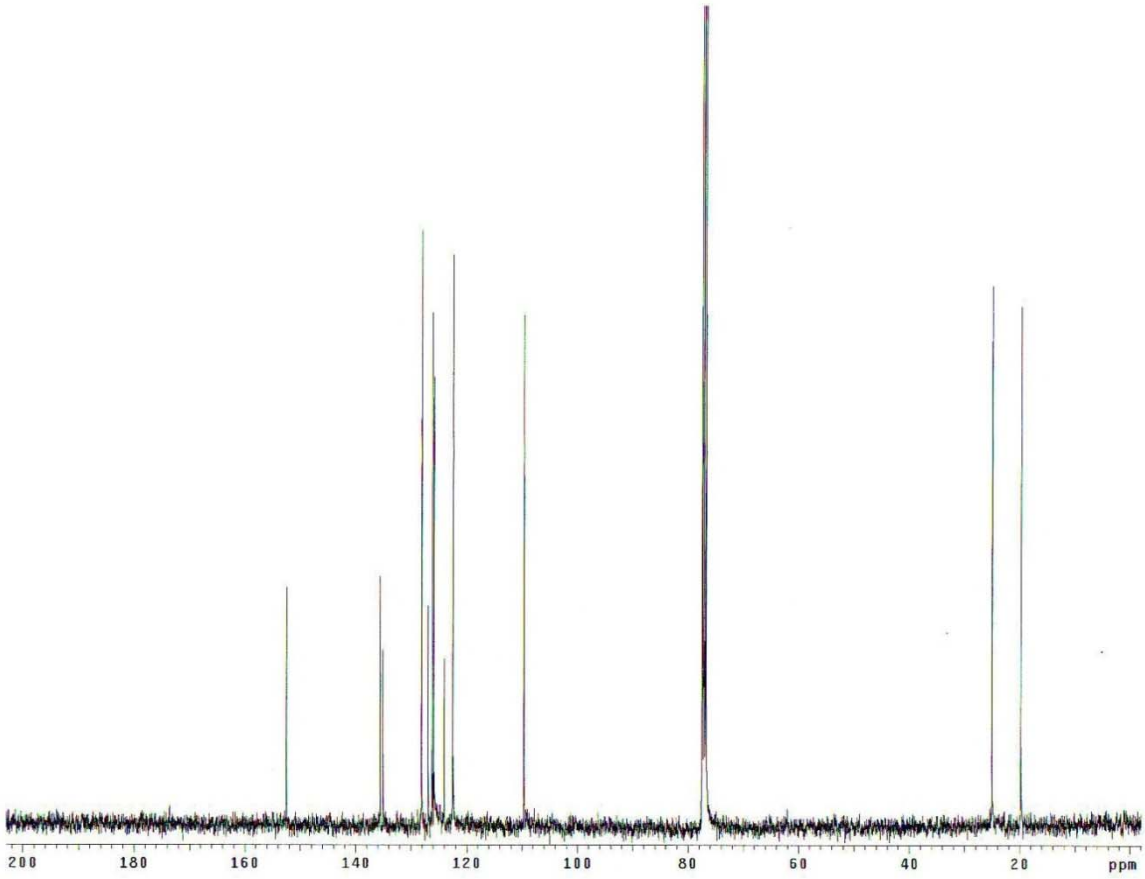
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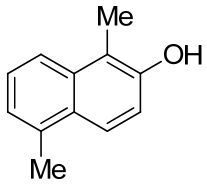
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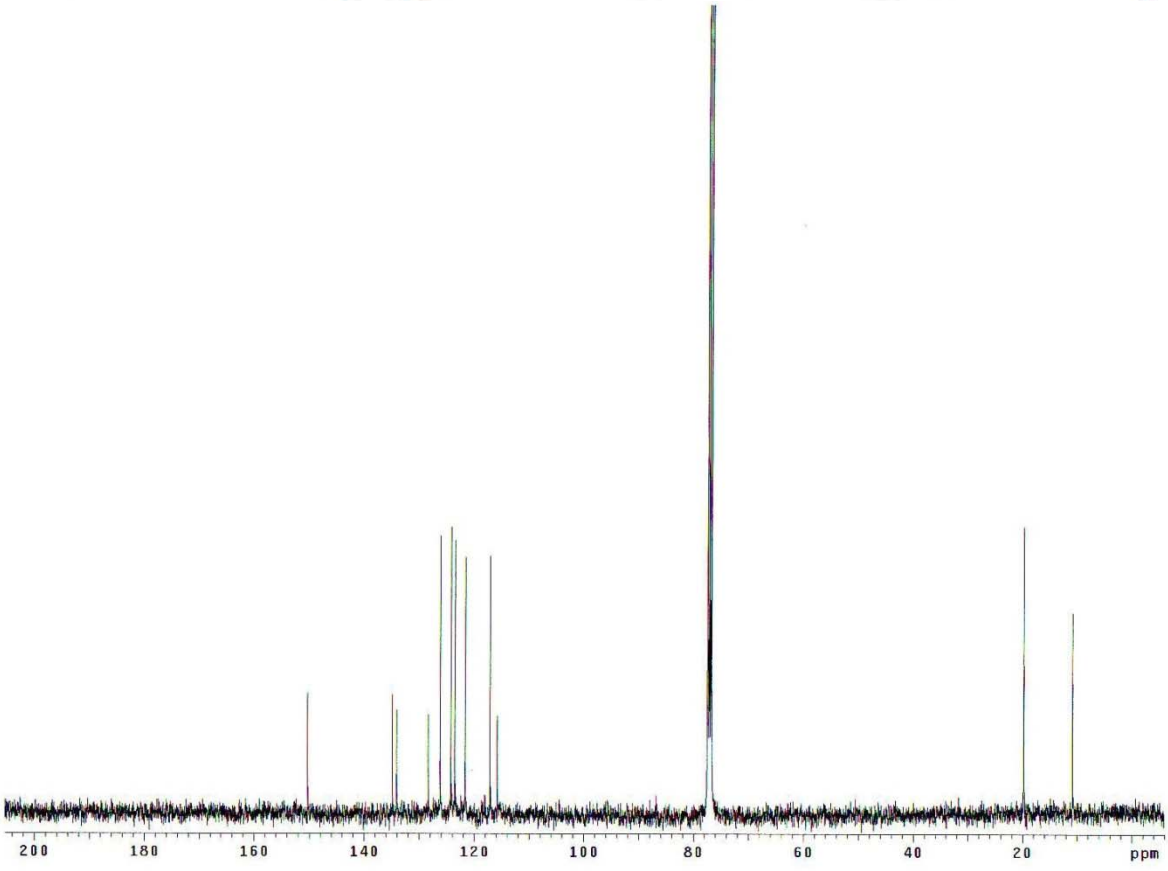
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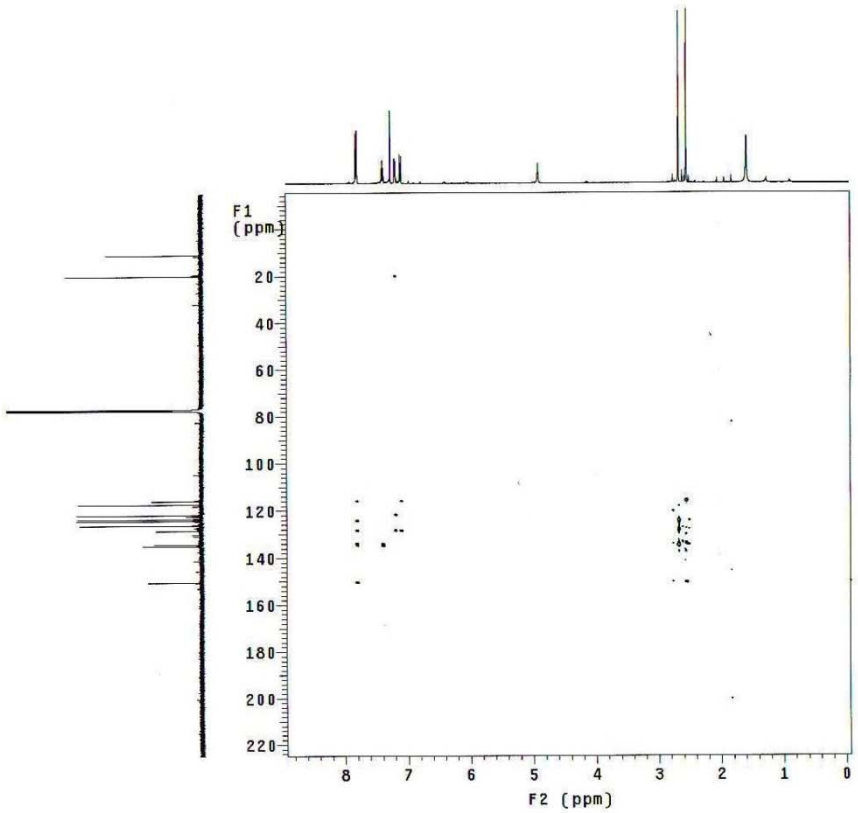

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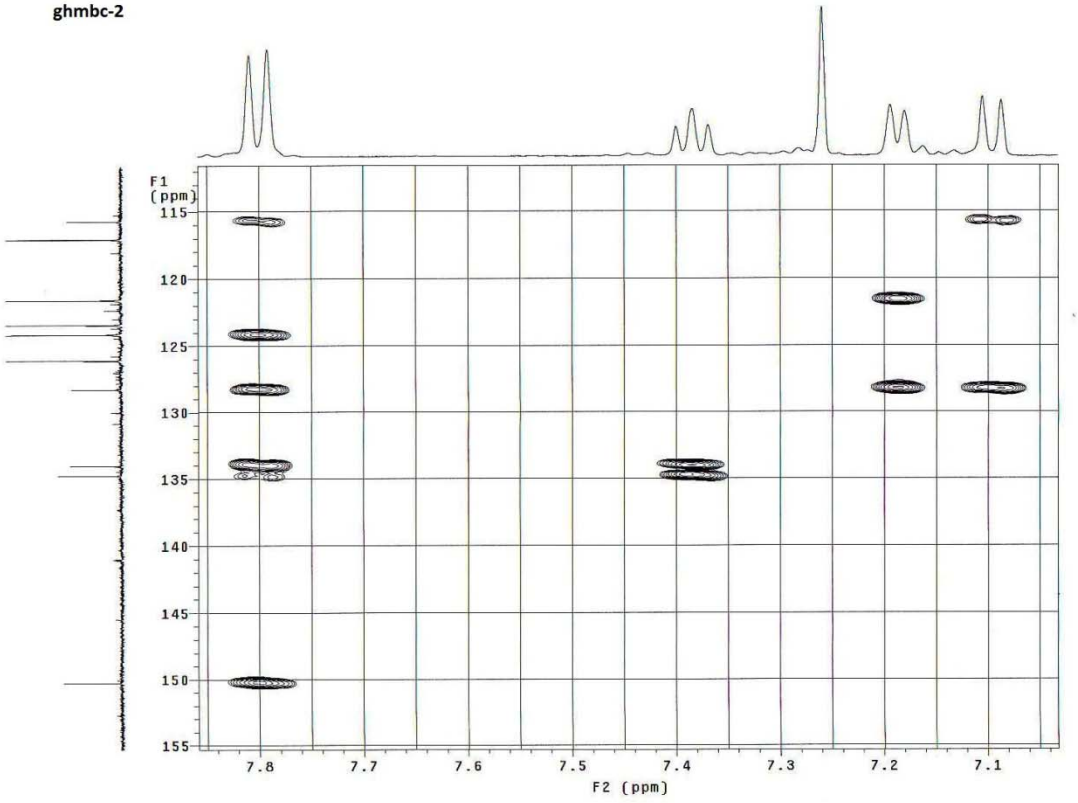

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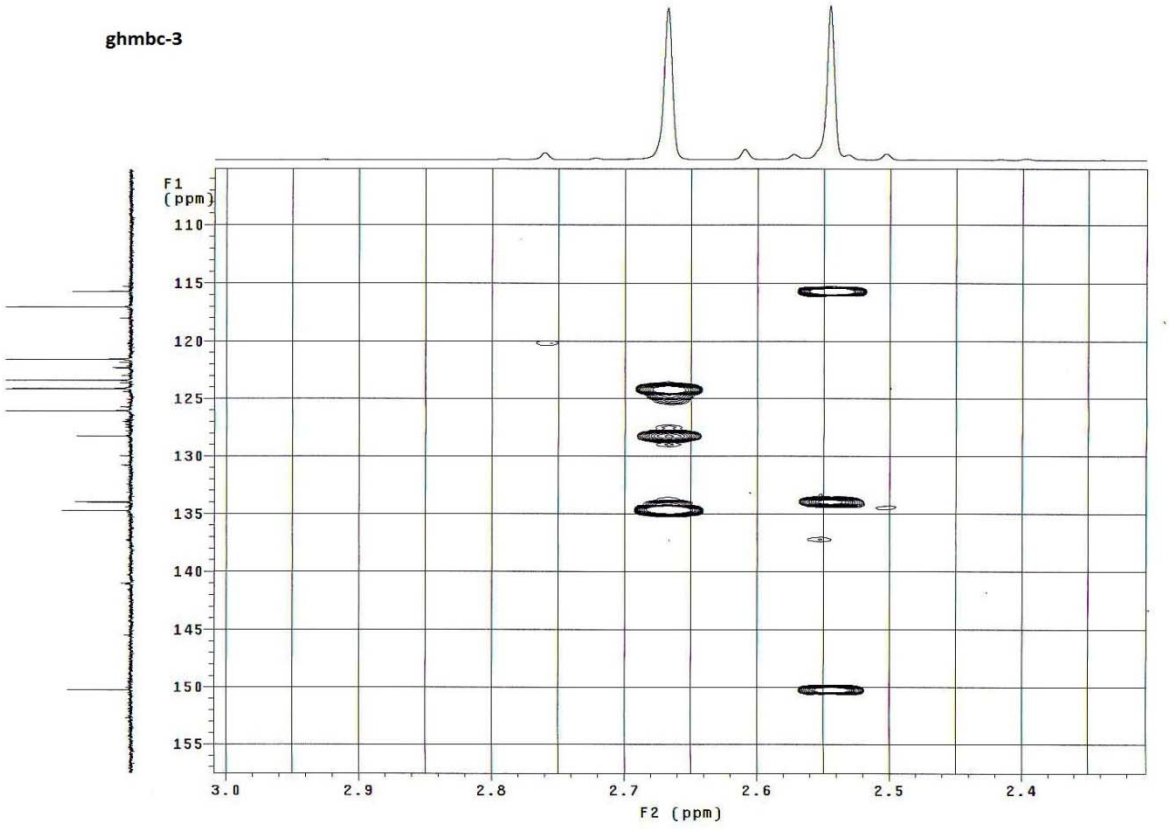

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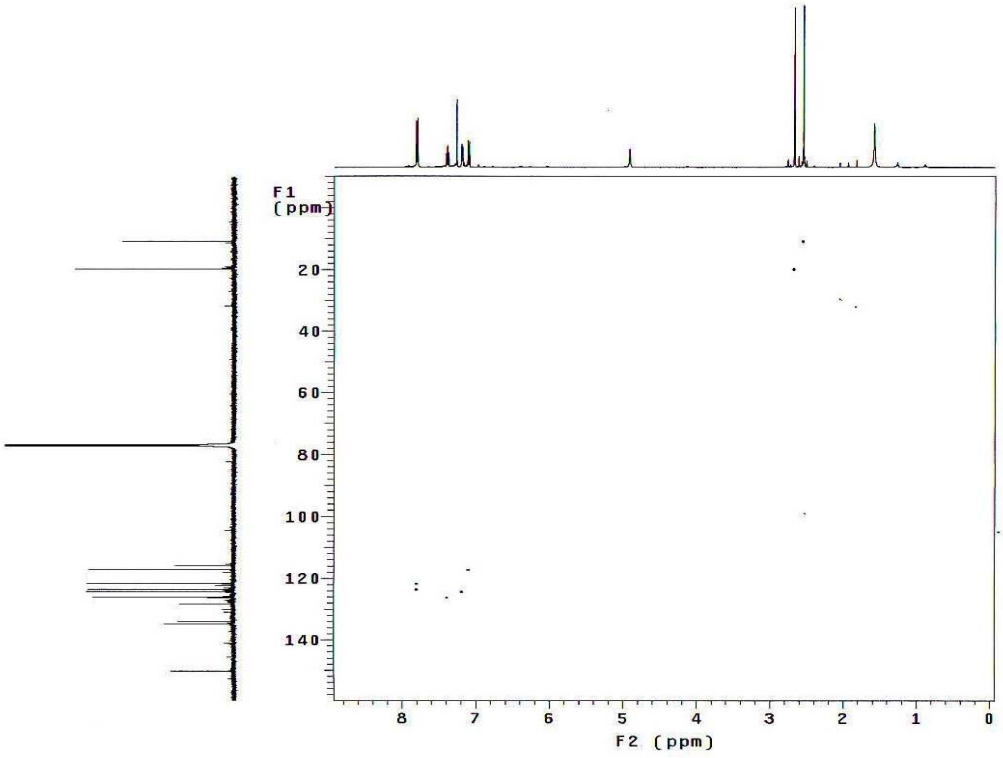

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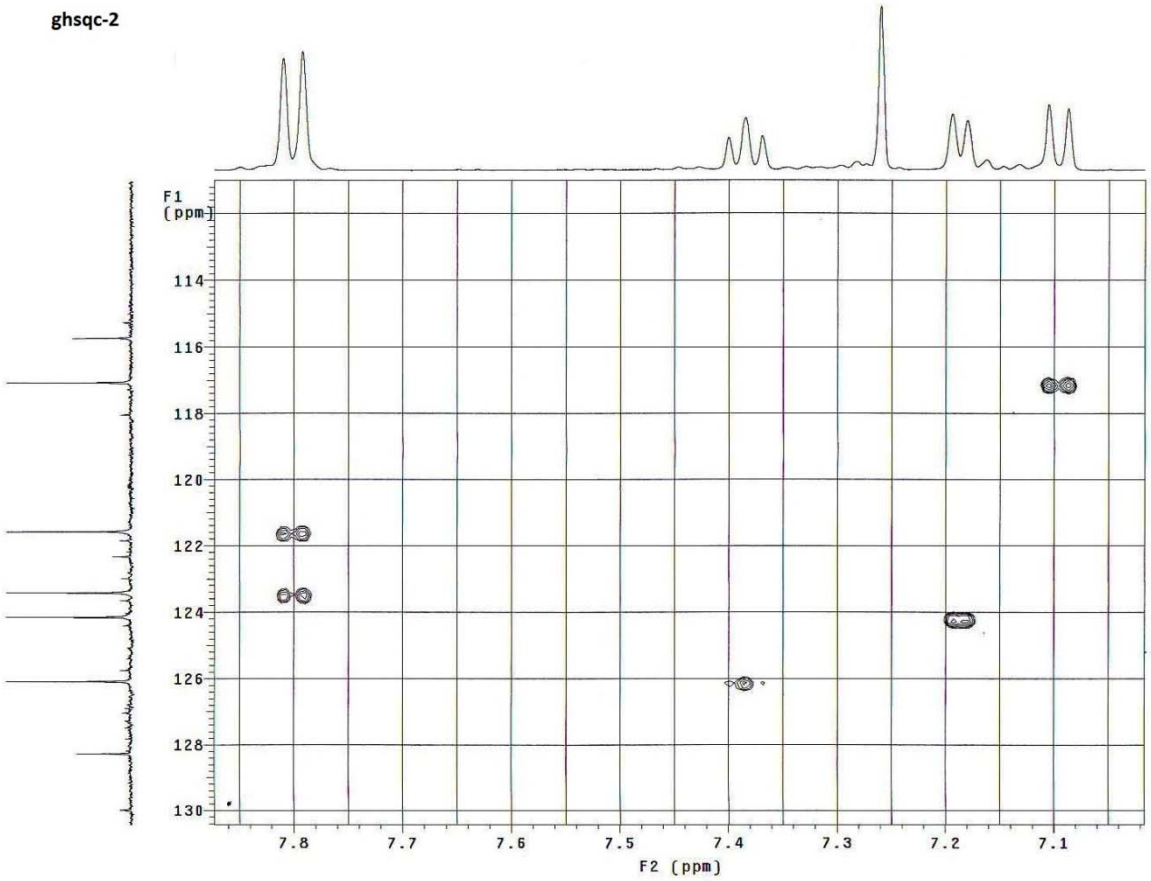

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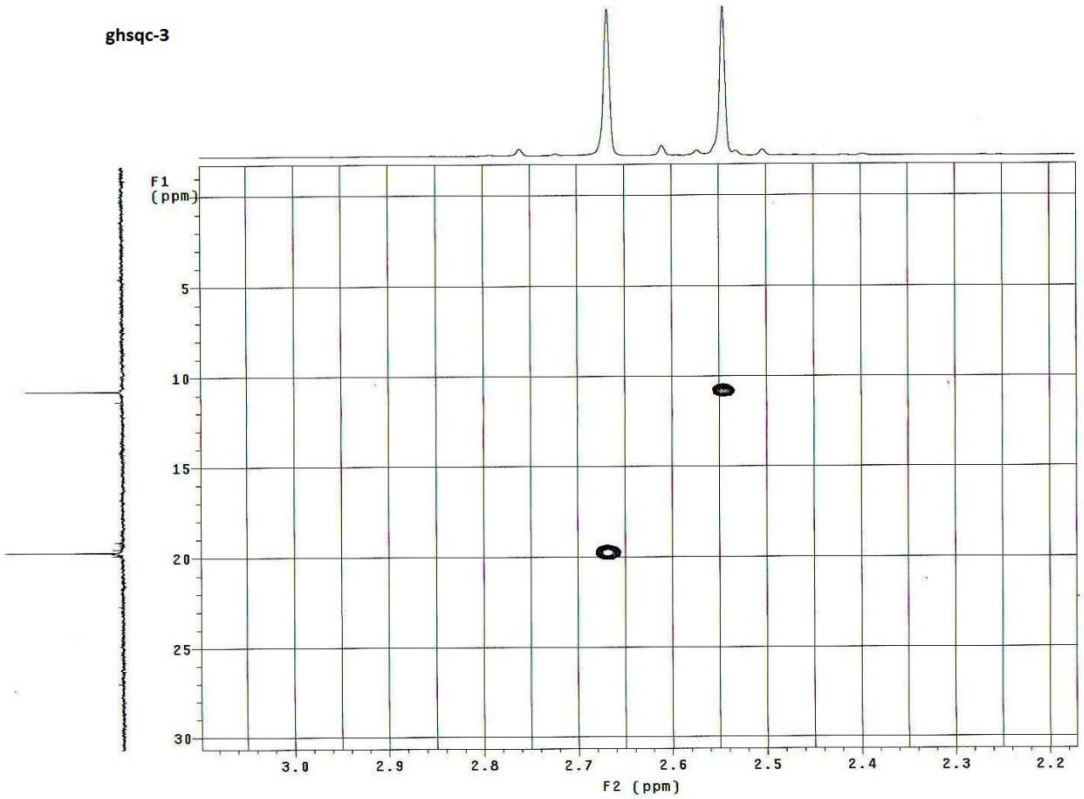

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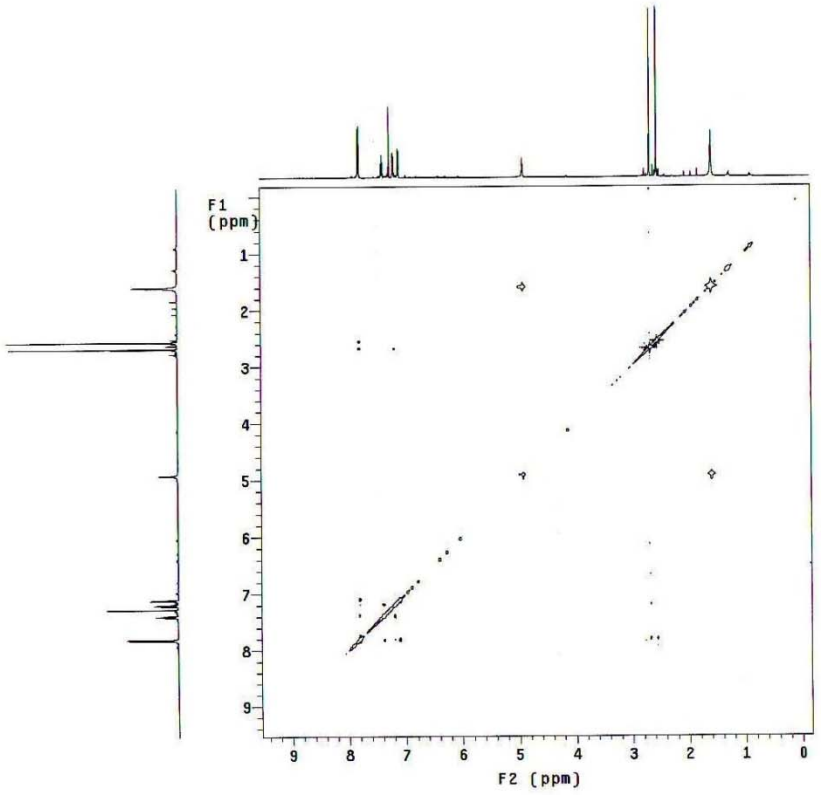

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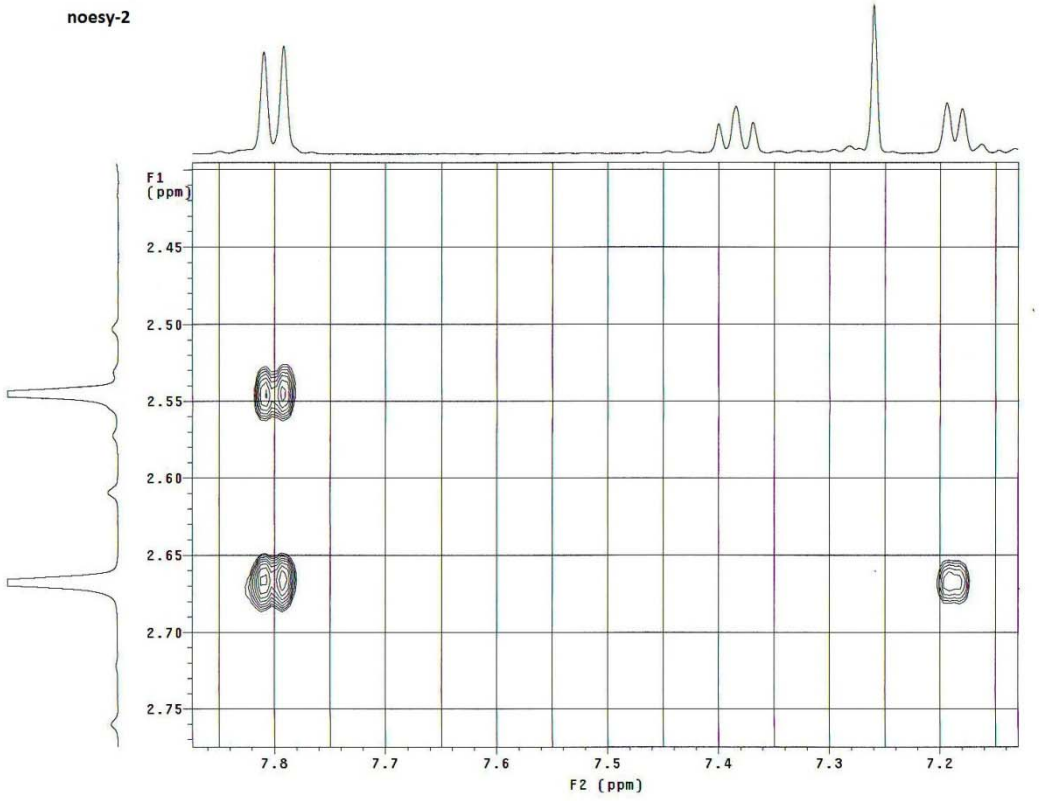

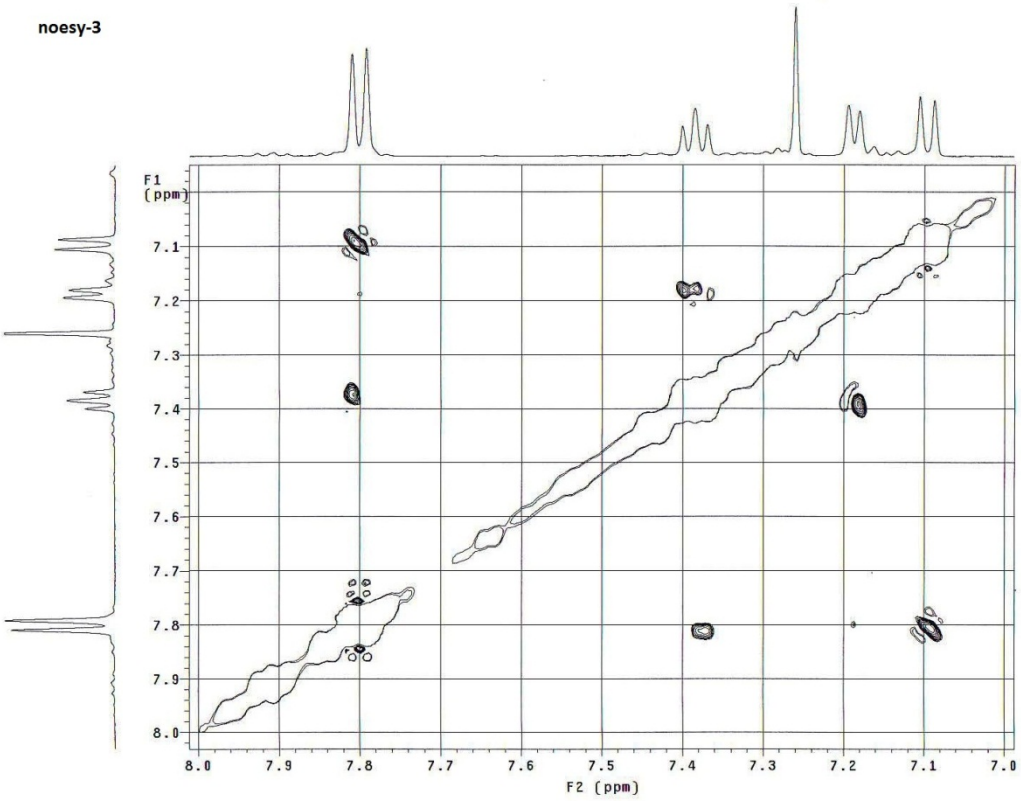
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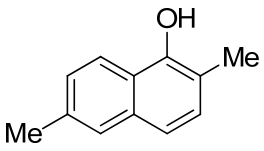
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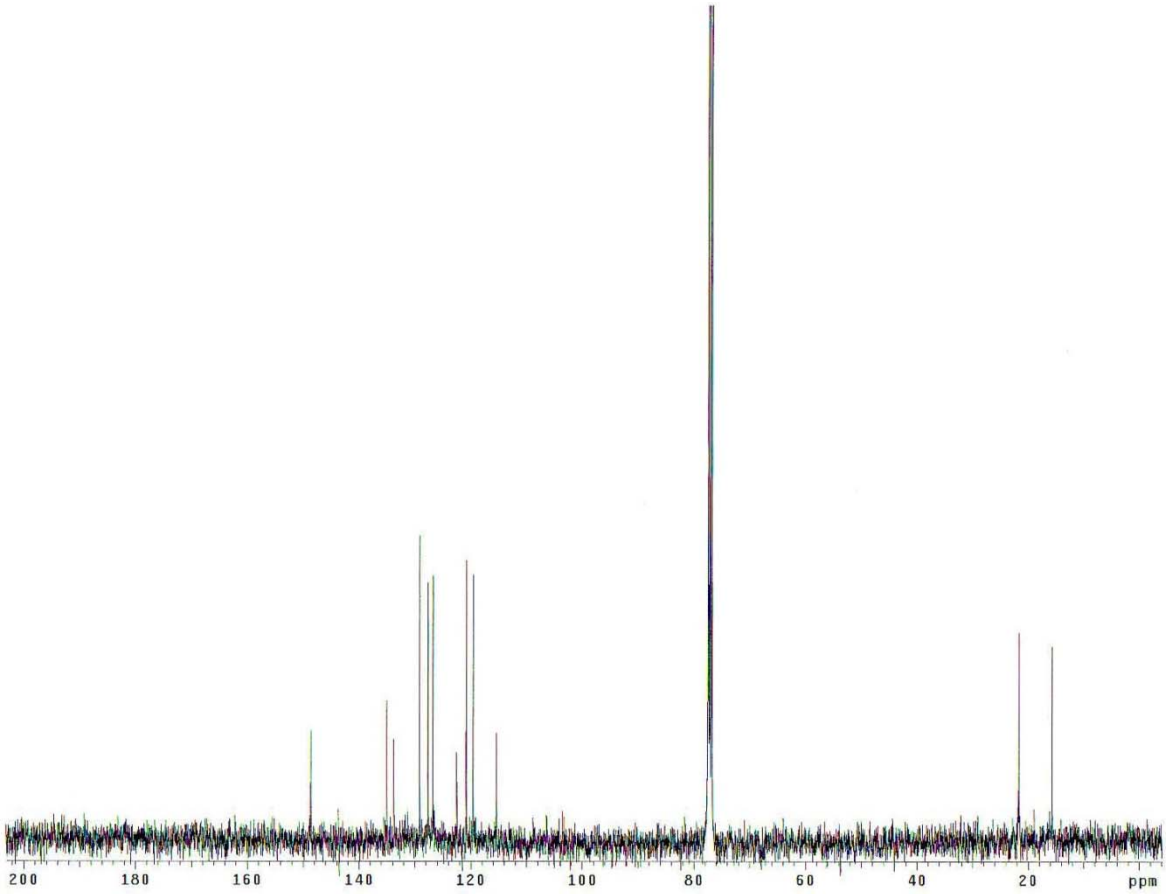
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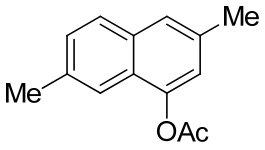
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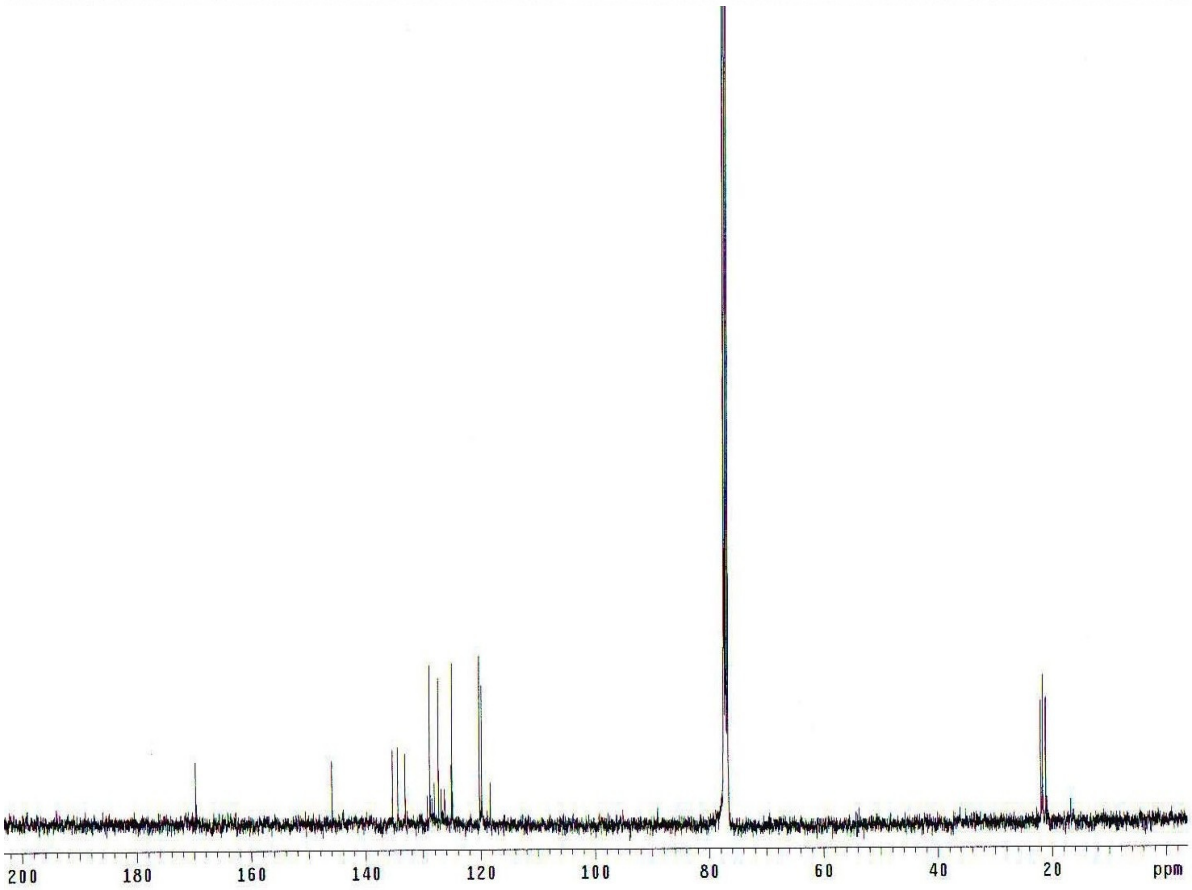
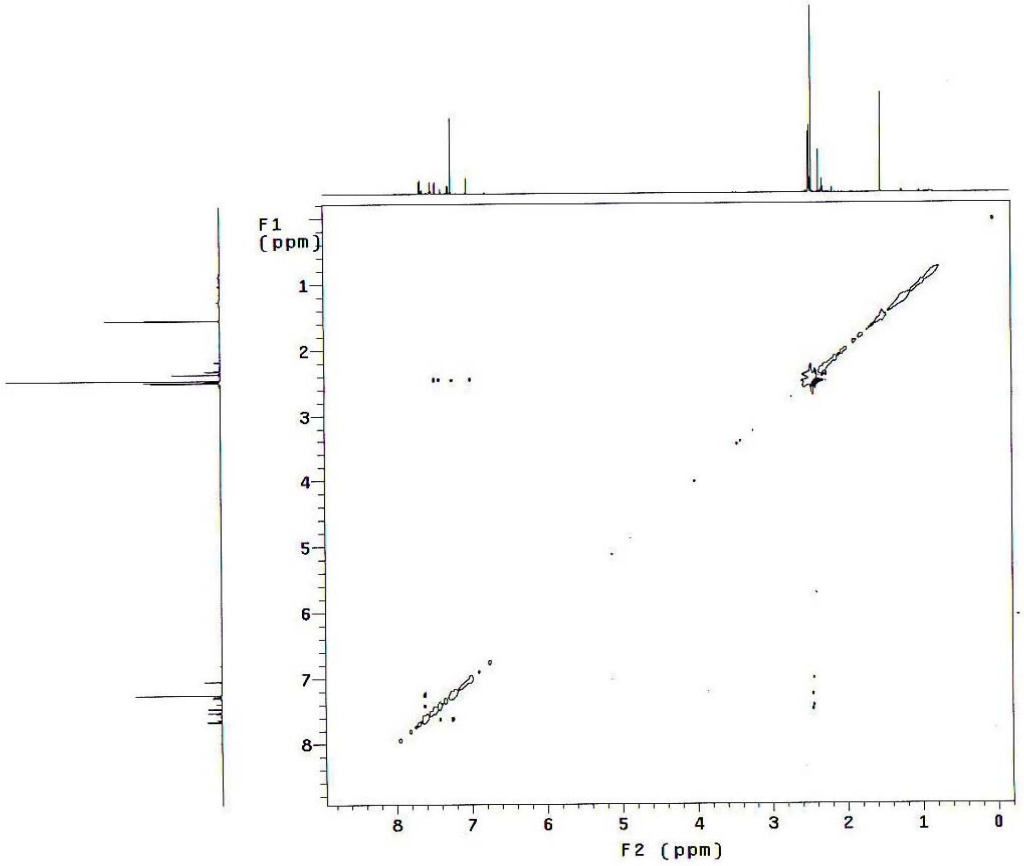
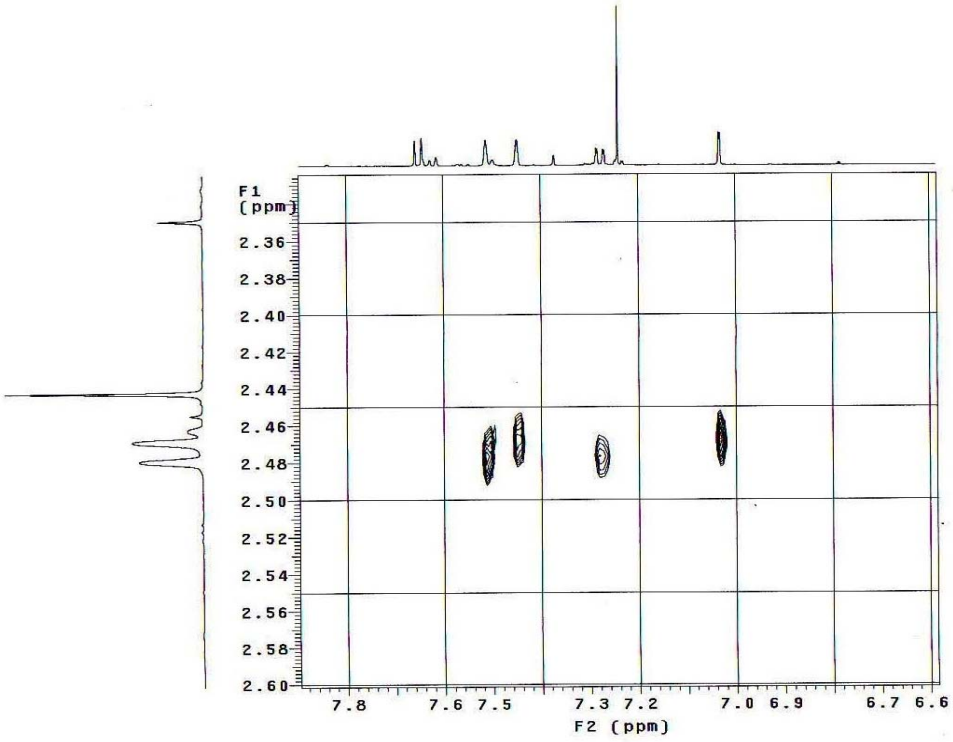
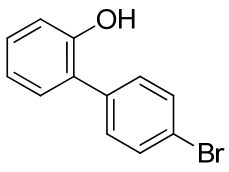
1
ppm

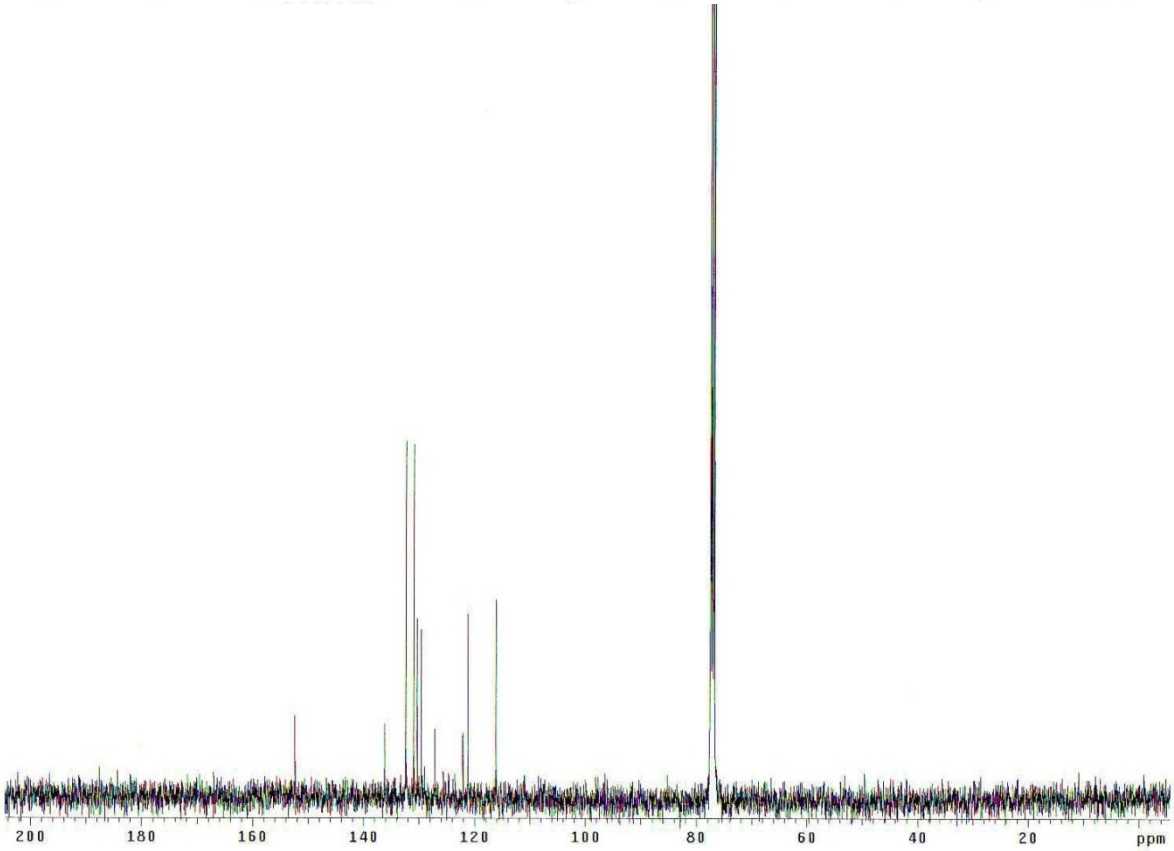

200
180
160
140
120
100
80
60
40
20
ppm

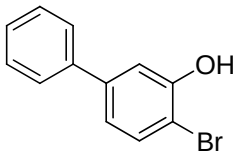

F1
(ppm)
1
2
3
4
5
6
7
8
8 7 6 5 4 3 2 1 0
F2 (ppm)


F1
(ppm)
2.36
2.38
2.40
2.42
2.44
2.46
2.48
2.50
2.52
2.54
2.56
2.58
2.60
7.8 7.6 7.5 7.3 7.2 7.0 6.9 6.7 6.6
F2 (ppm)

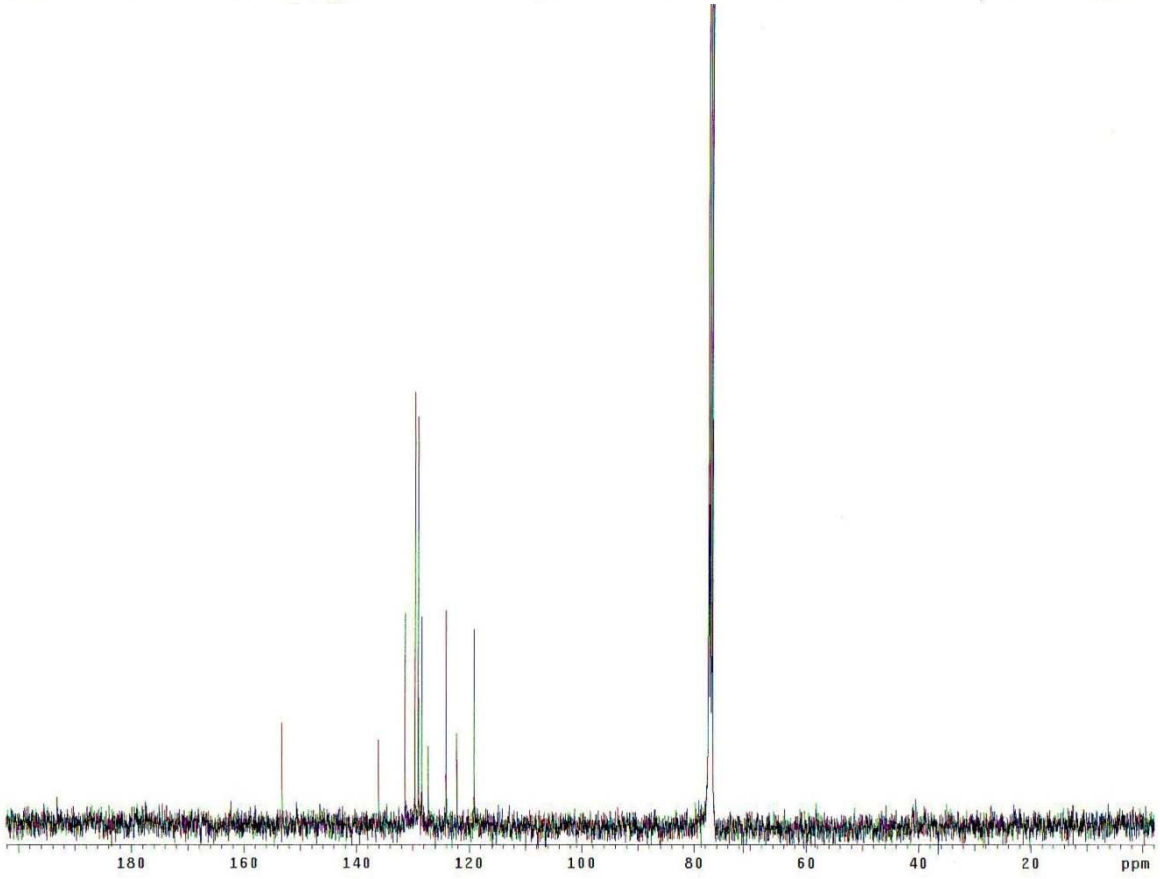

OH
Br

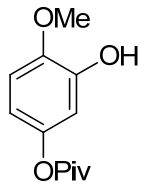
10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

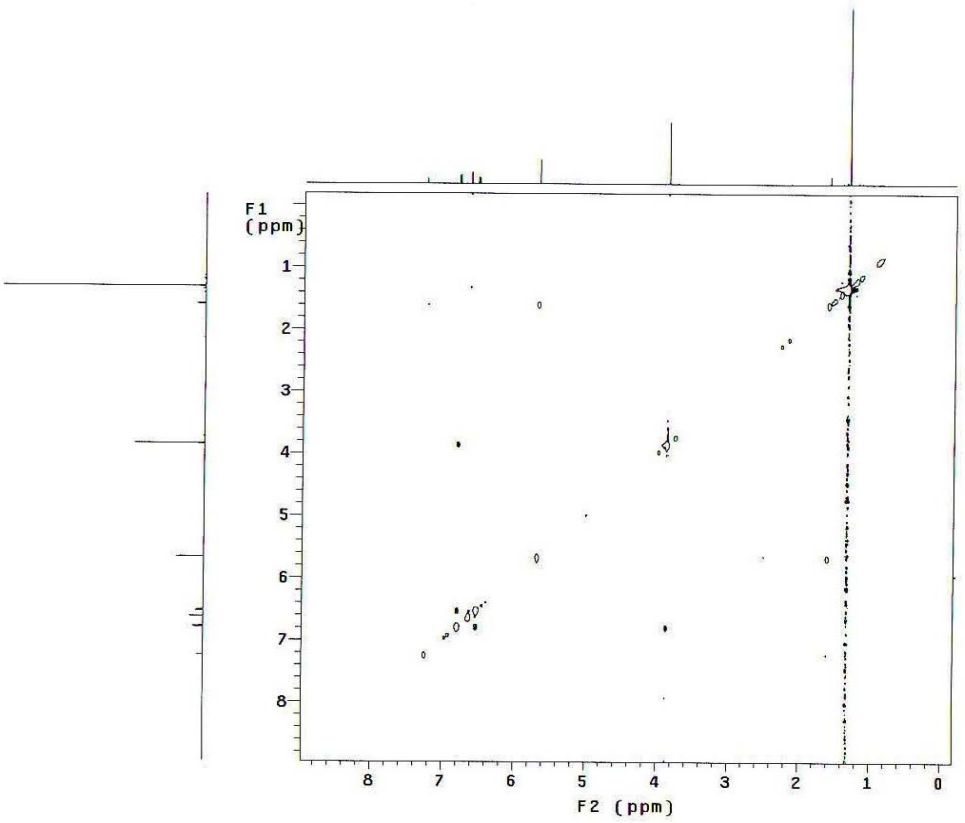

OH
Br

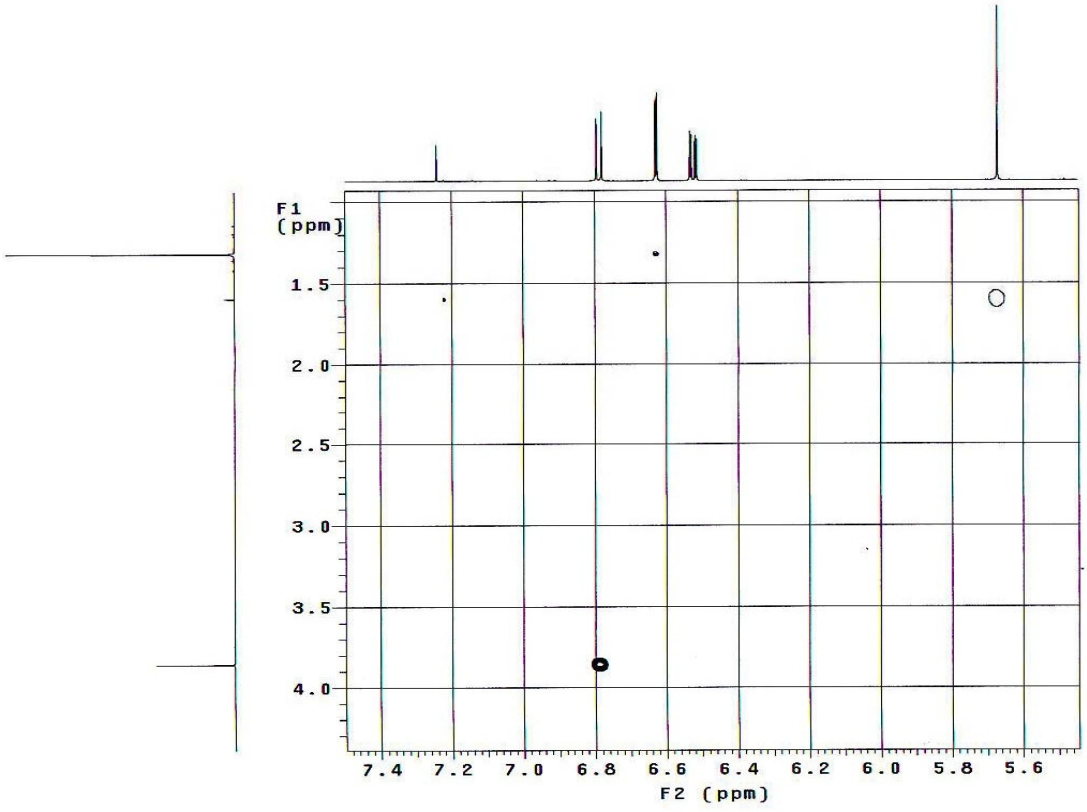
10
9
8
7
6
5
4
3
2
1
ppm

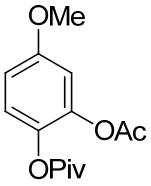

180
160
140
120
100
80
60
40
20
ppm


OMe
OH
OPiv

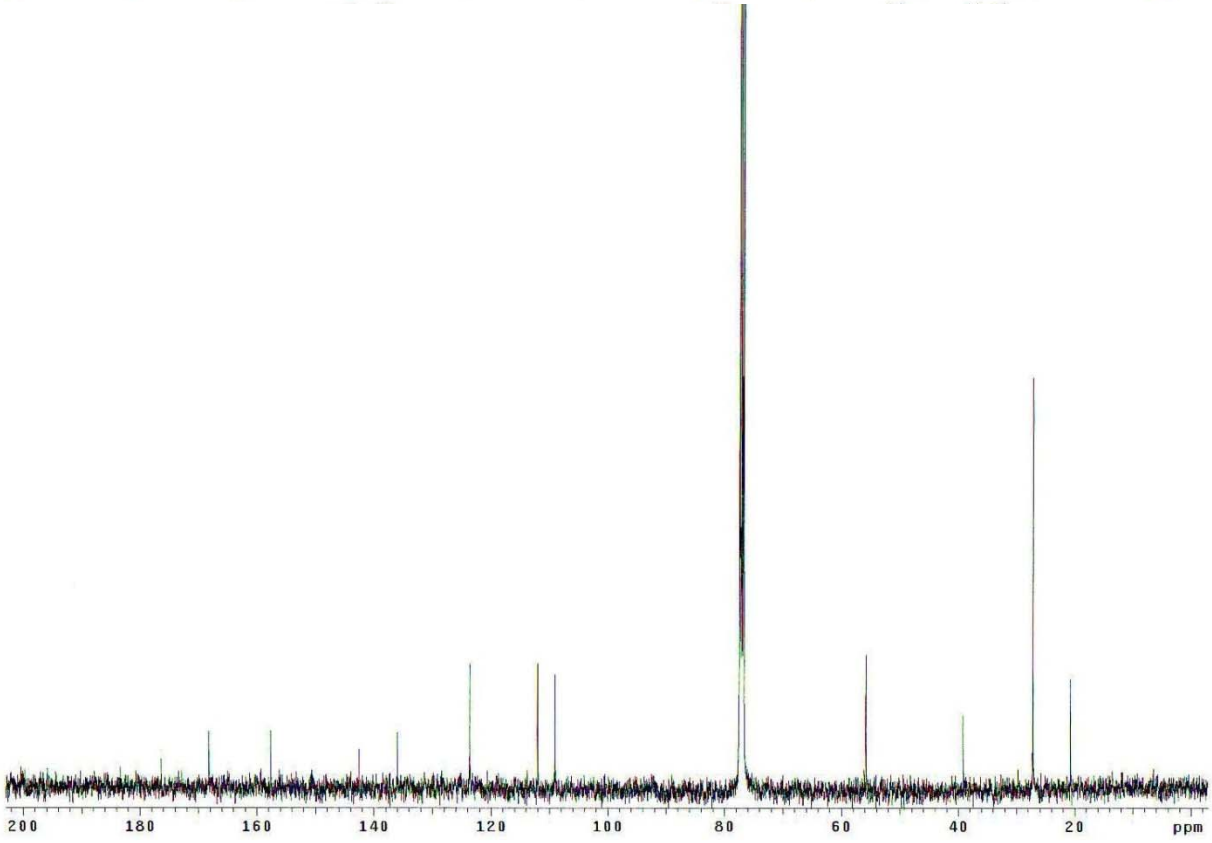
10
9
8
7
6
5
4
3
2
1
ppm
180
160
140
120
100
80
60
40
20
ppm

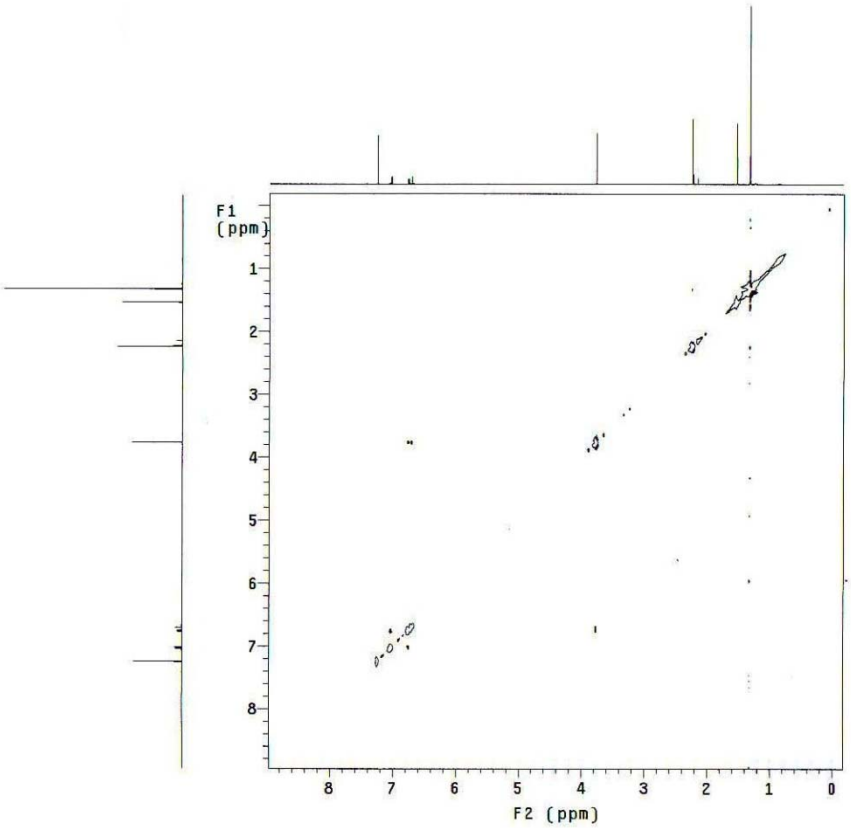

F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)

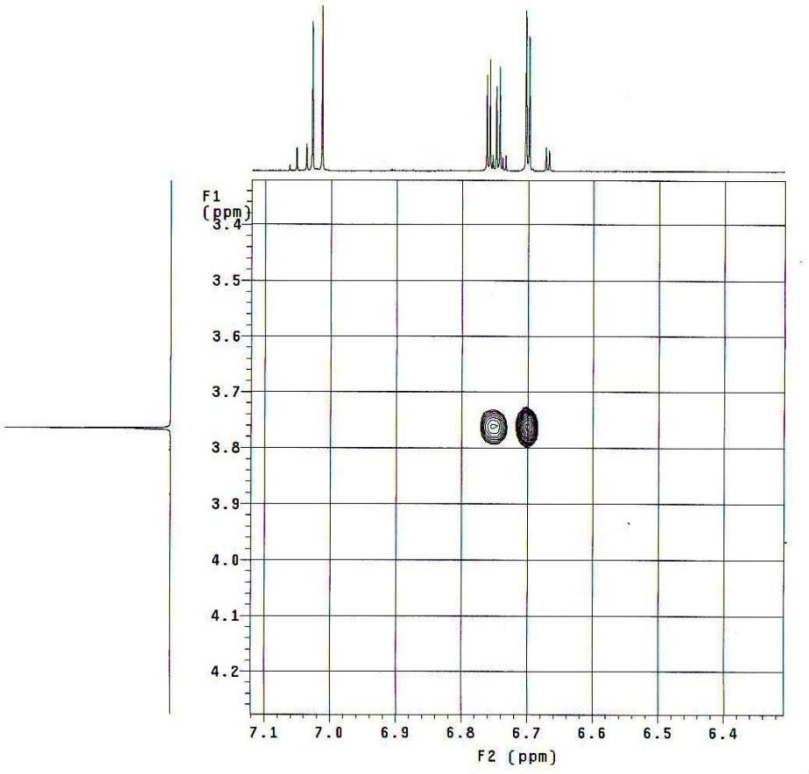

F1
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
F2 (ppm)

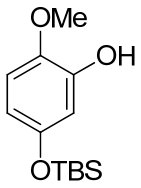

OMe
OAc
OPiv

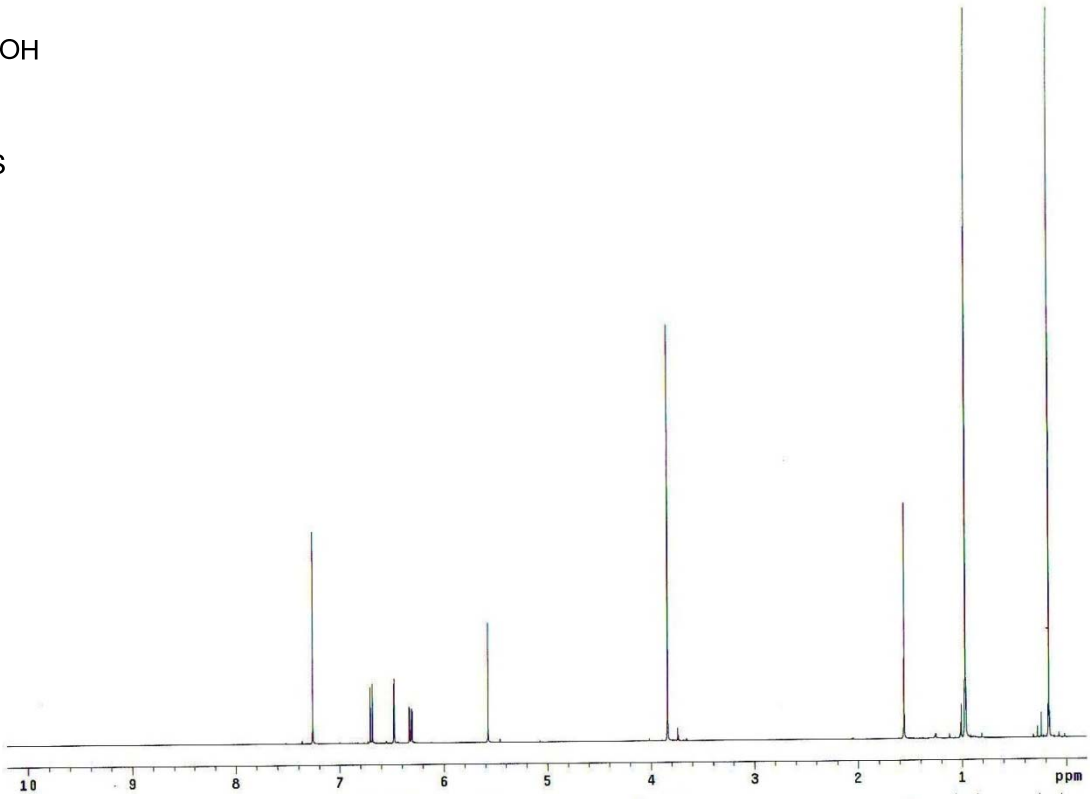
10
9
8
7
6
5
4
3
2
1
ppm

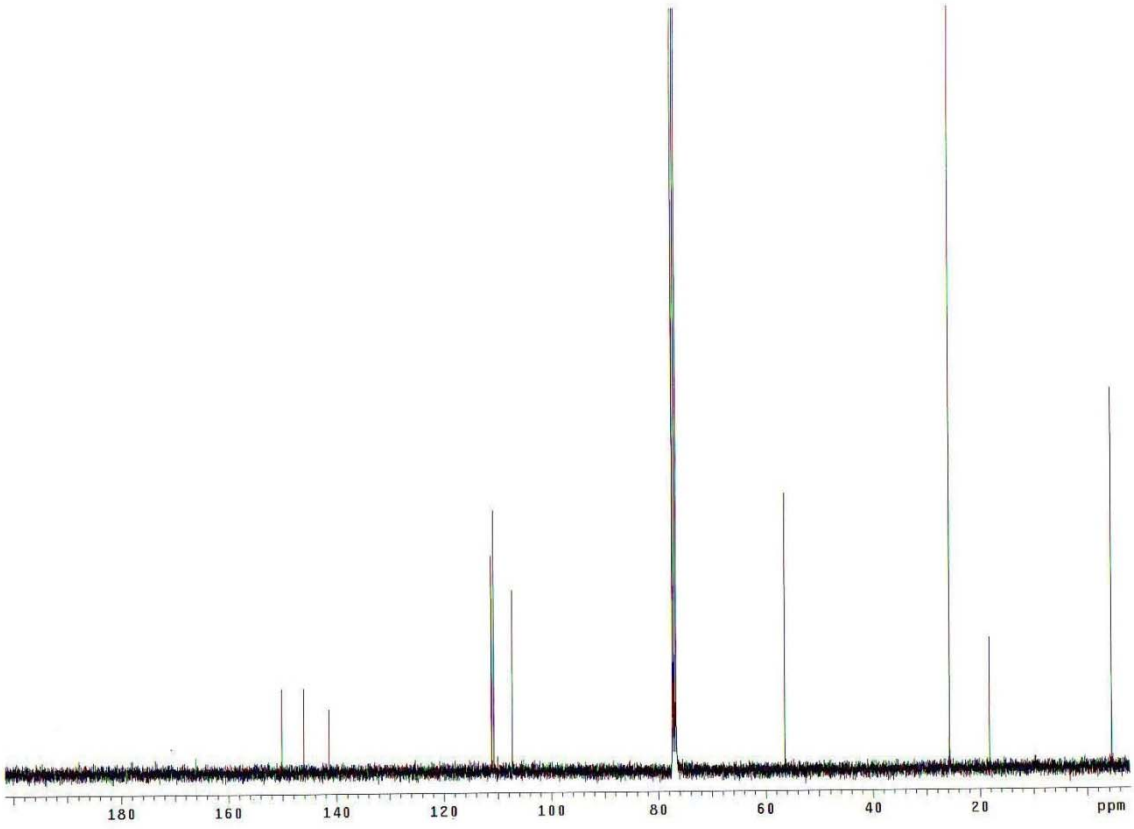

200
180
160
140
120
100
80
60
40
20
ppm

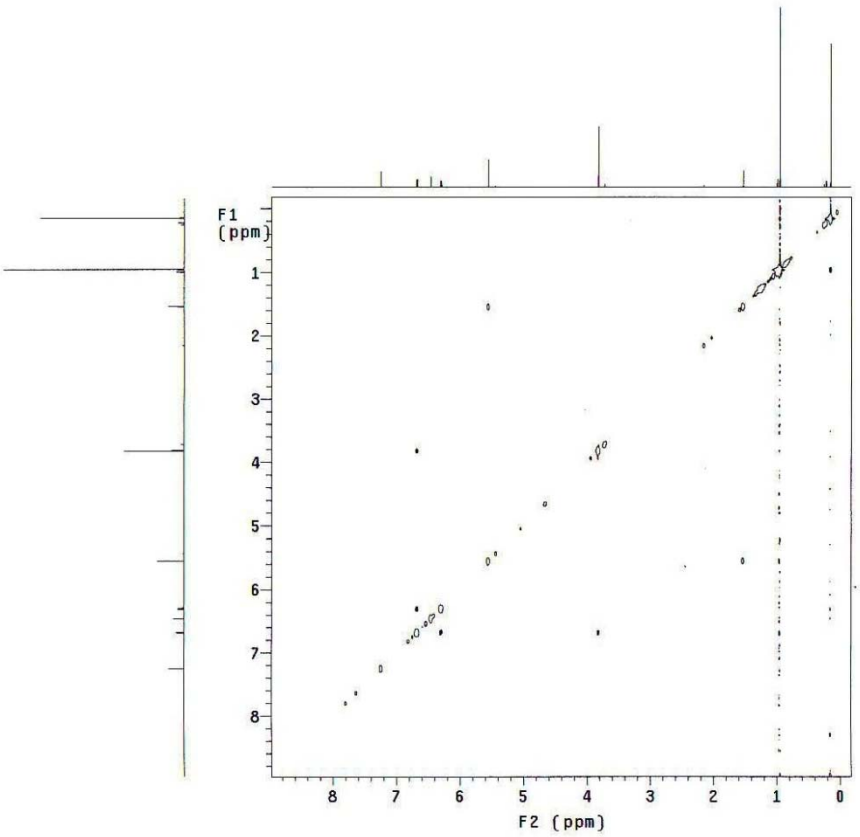

F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)

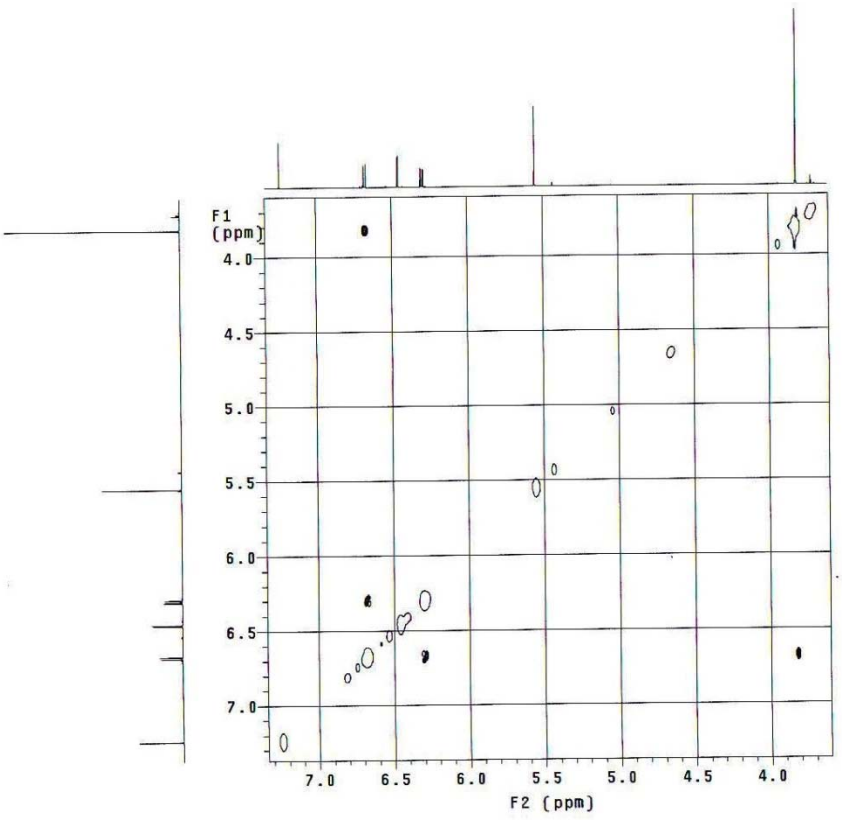

F1
(ppm)
3.4
3.5
3.6
3.7
3.8
3.9
4.0
4.1
4.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
F2 (ppm)

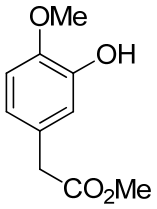

OMe
OH
OTBS


10
9
8
7
6
5
4
3
2
1
ppm

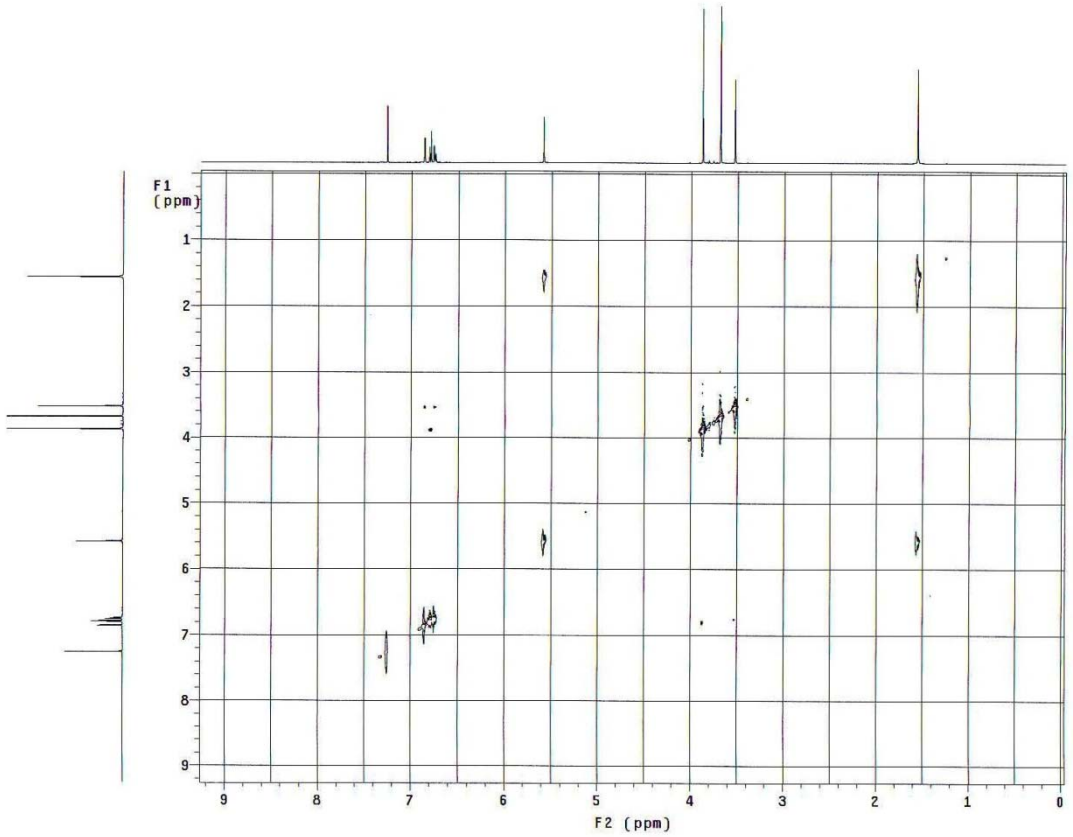

180
160
140
120
100
80
60
40
20
ppm

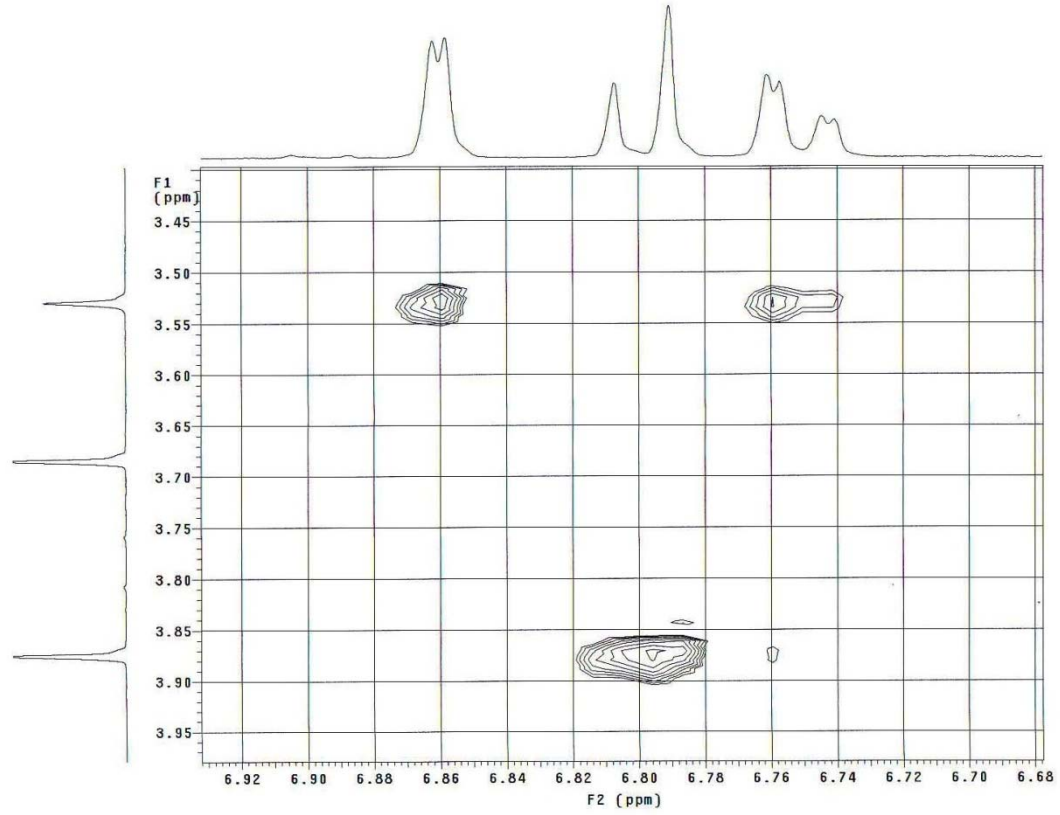

F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)

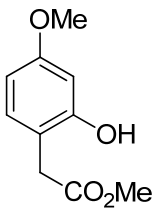

F1
(ppm)
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
F2 (ppm)

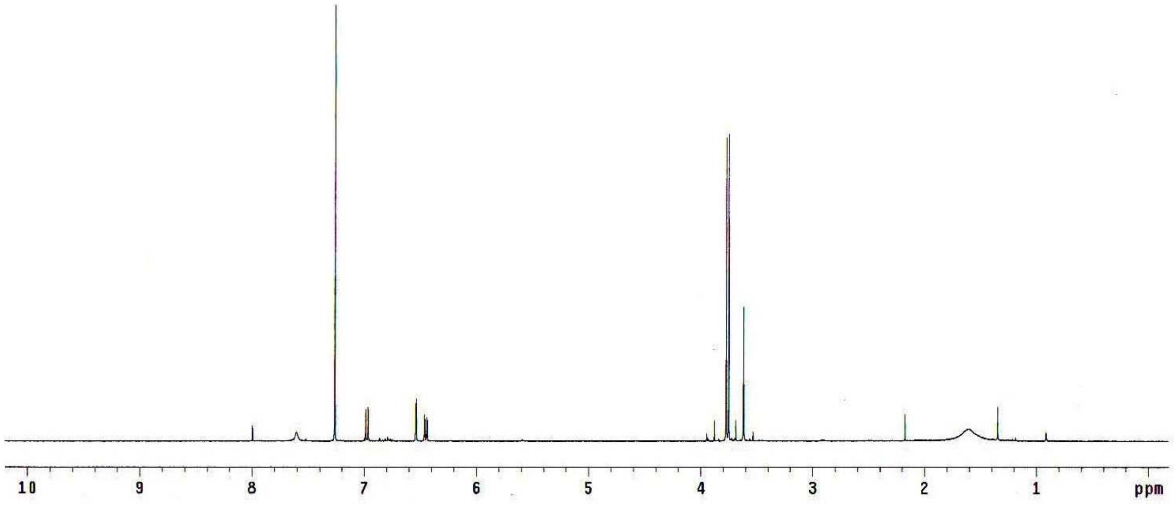

OMe
OH
CO2Me

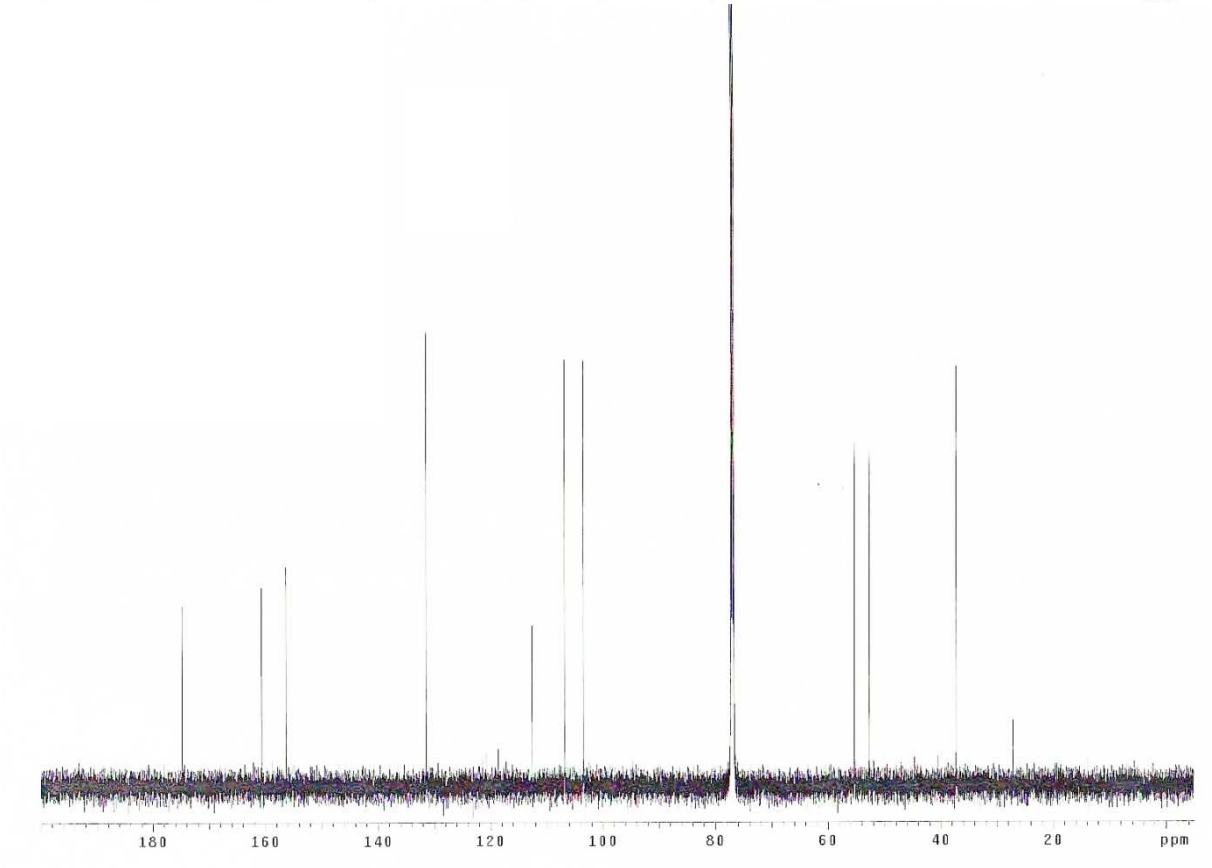
10
9
8
7
6
5
4
3
2
1
ppm
200
180
160
140
120
100
80
60
40
20
ppm

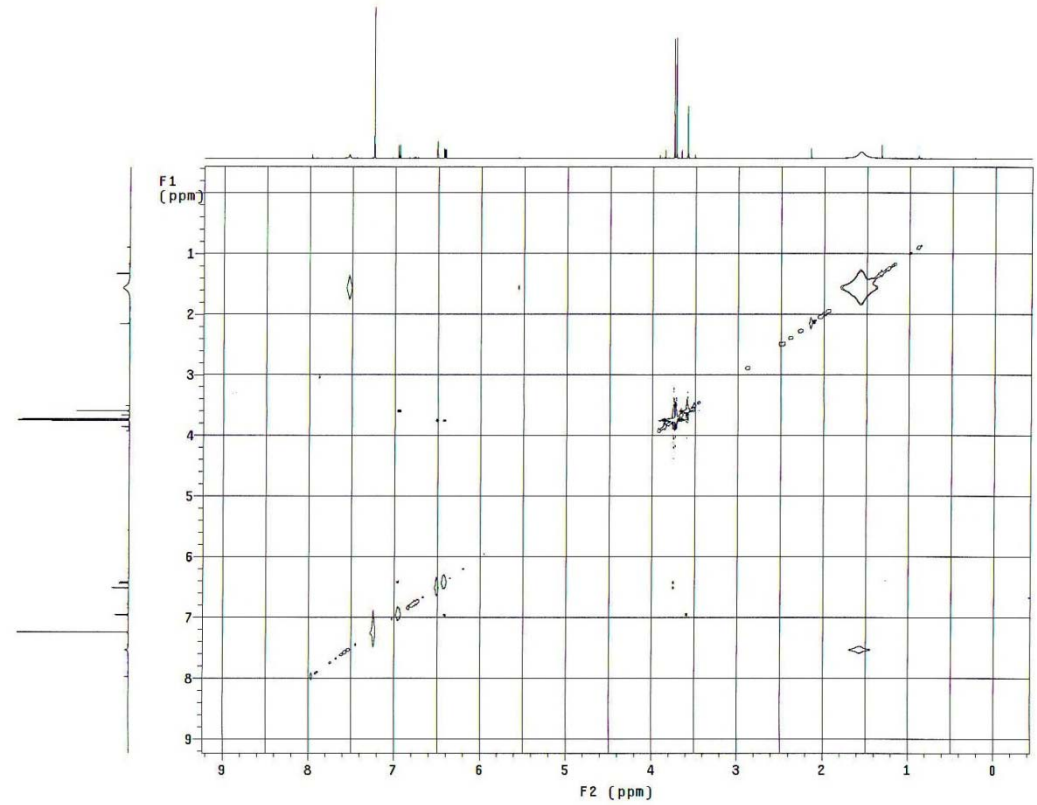

F1
(ppm)
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
0
F2 (ppm)

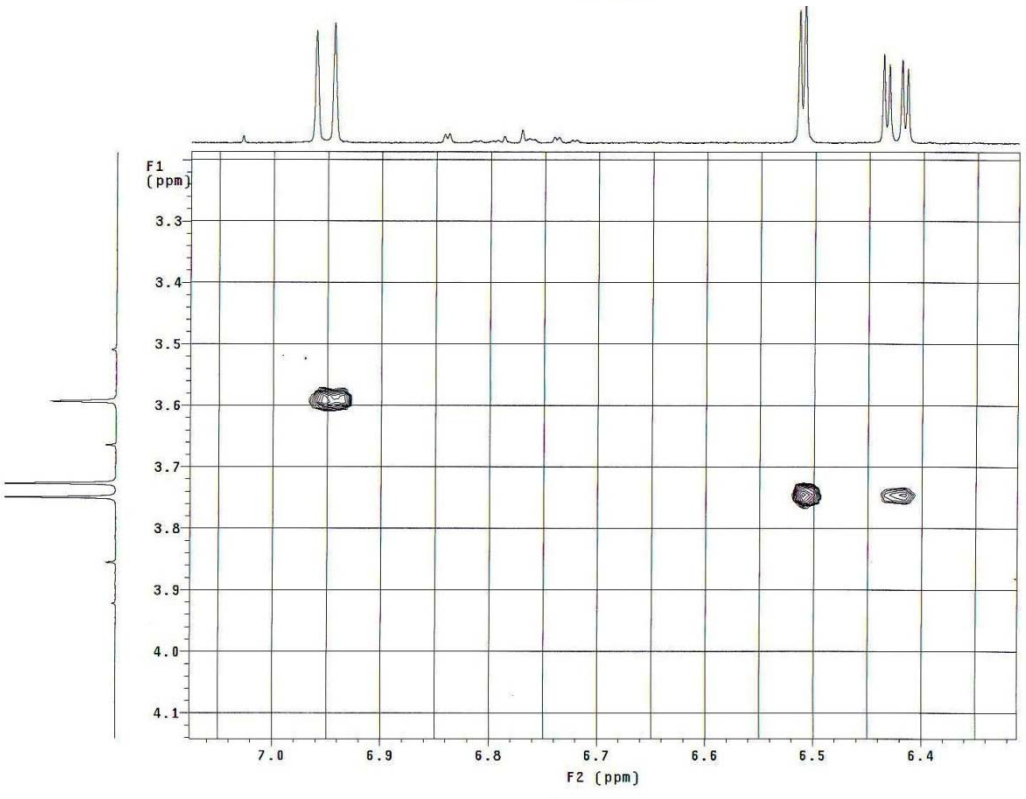

F1
(ppm)
3.45
3.50
3.55
3.60
3.65
3.70
3.75
3.80
3.85
3.90
3.95
6.92
6.90
6.88
6.86
6.84
6.82
6.80
6.78
6.76
6.74
6.72
6.70
6.68
F2 (ppm)

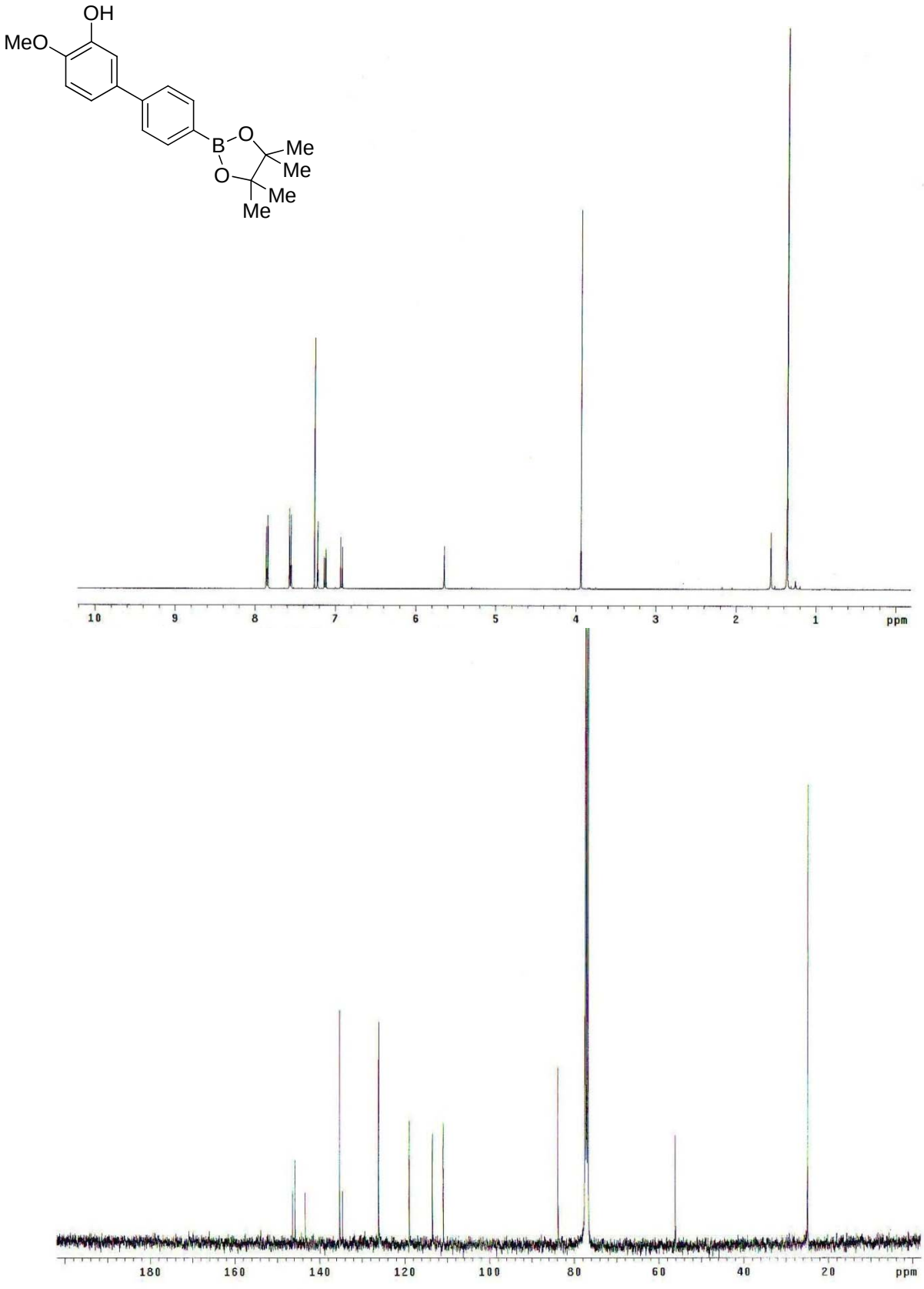

OMe
OH
CO2Me

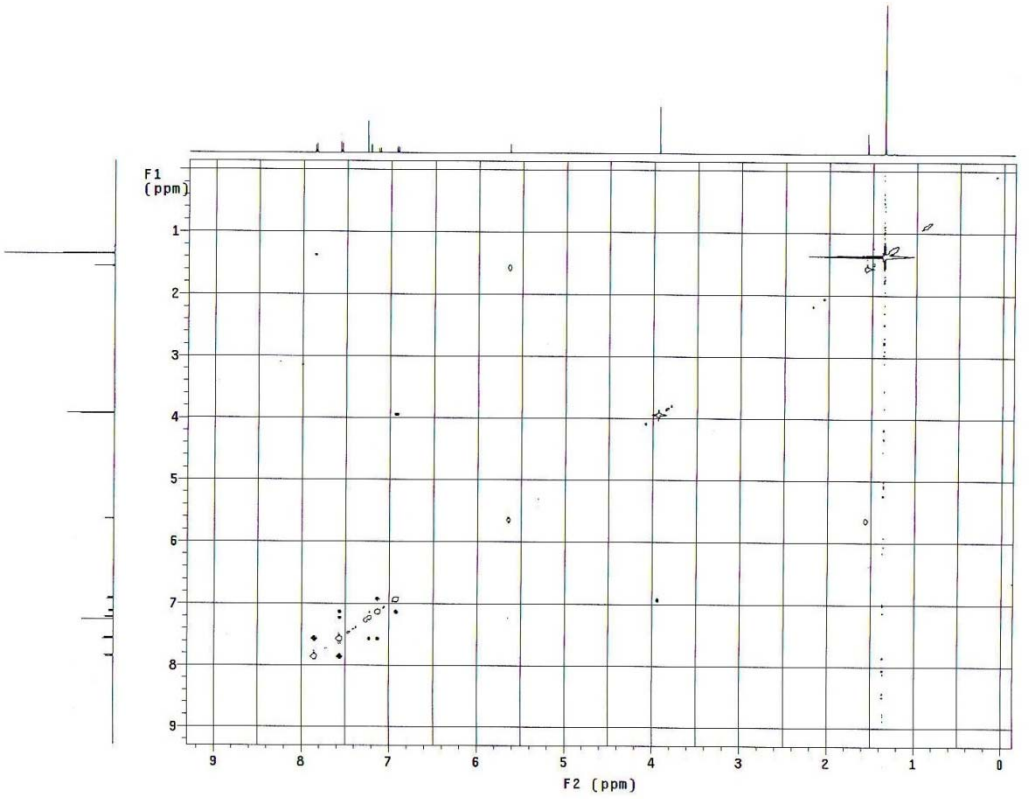

10
9
8
7
6
5
4
3
2
1
ppm

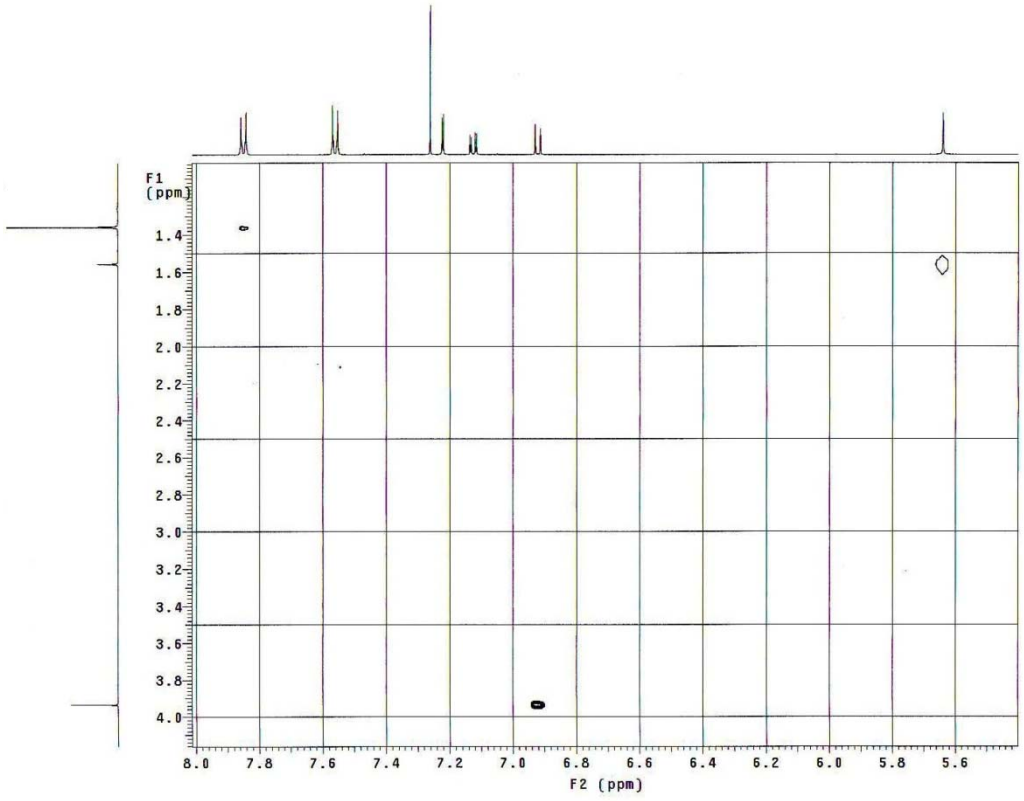

180
160
140
120
100
80
60
40
20
ppm

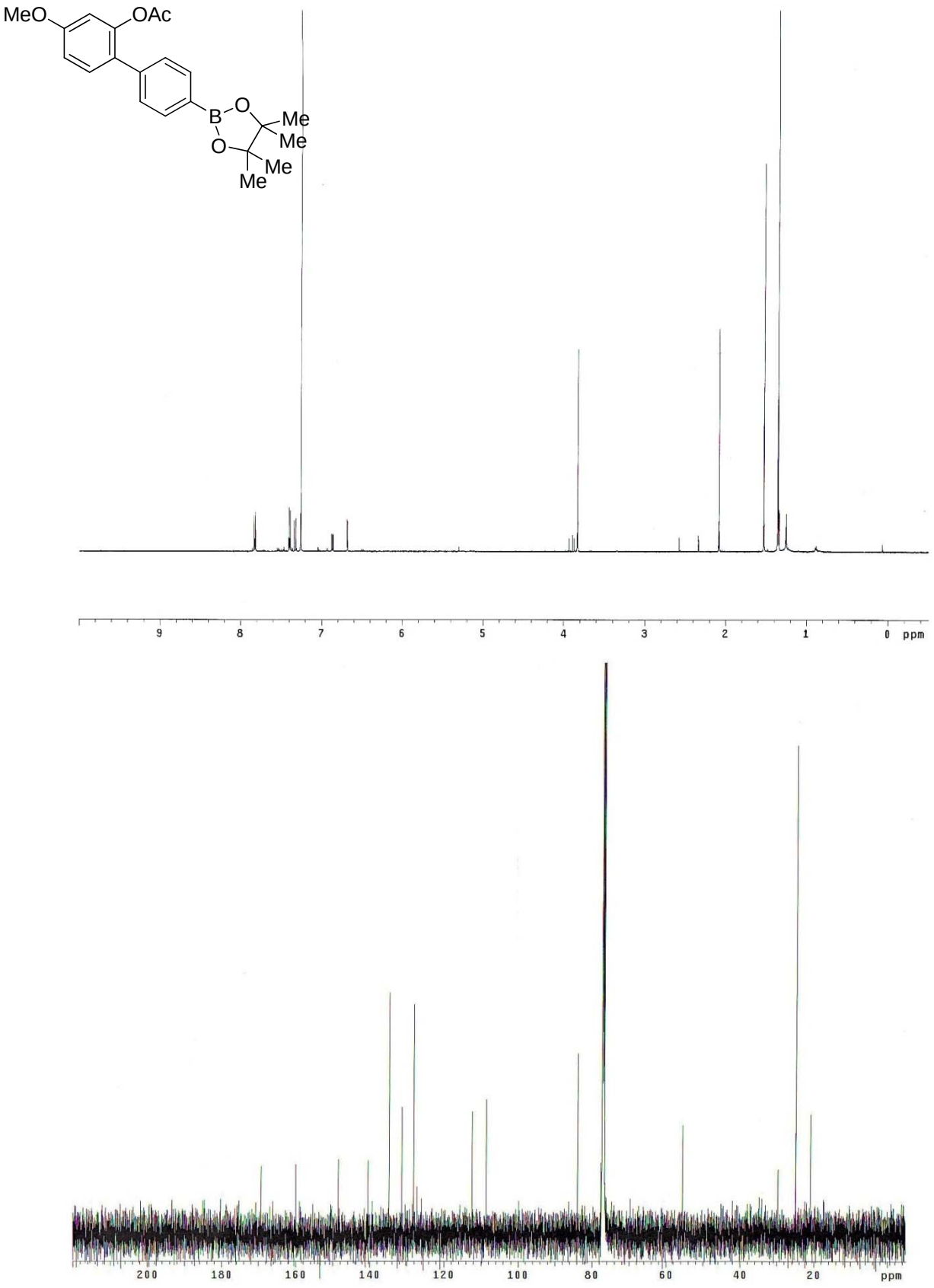

F1
(ppm)
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
0
F2 (ppm)

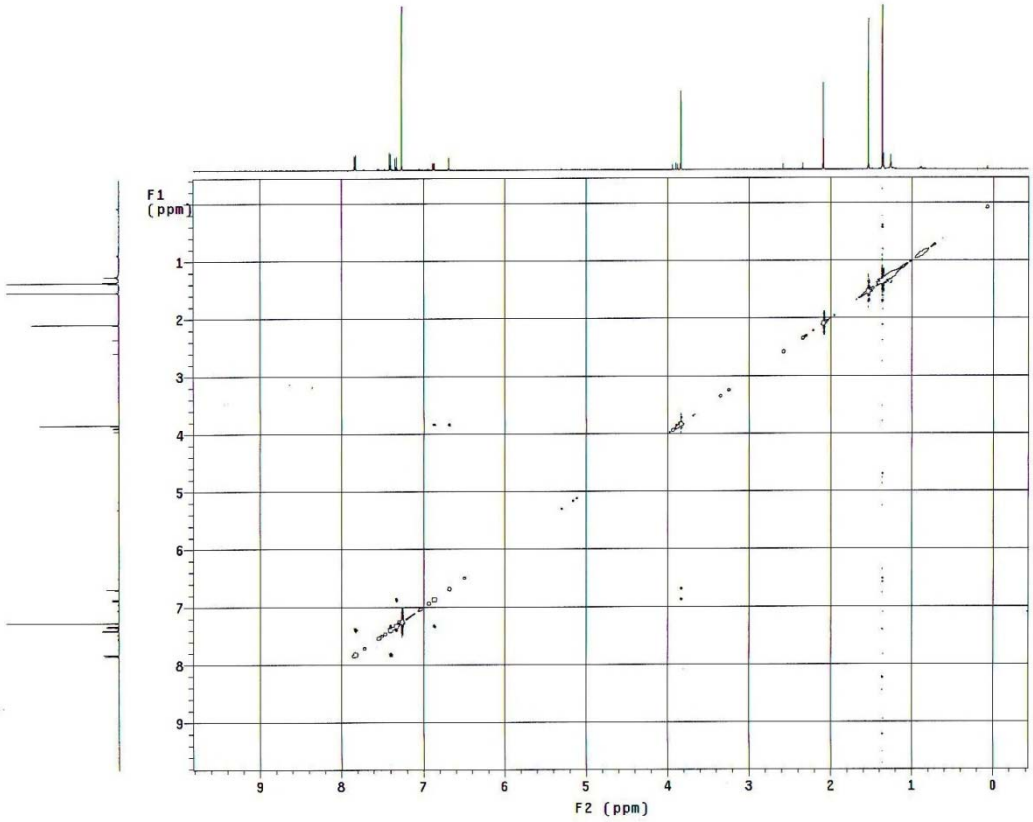

F1
(ppm)
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4.0
4.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
F2 (ppm)

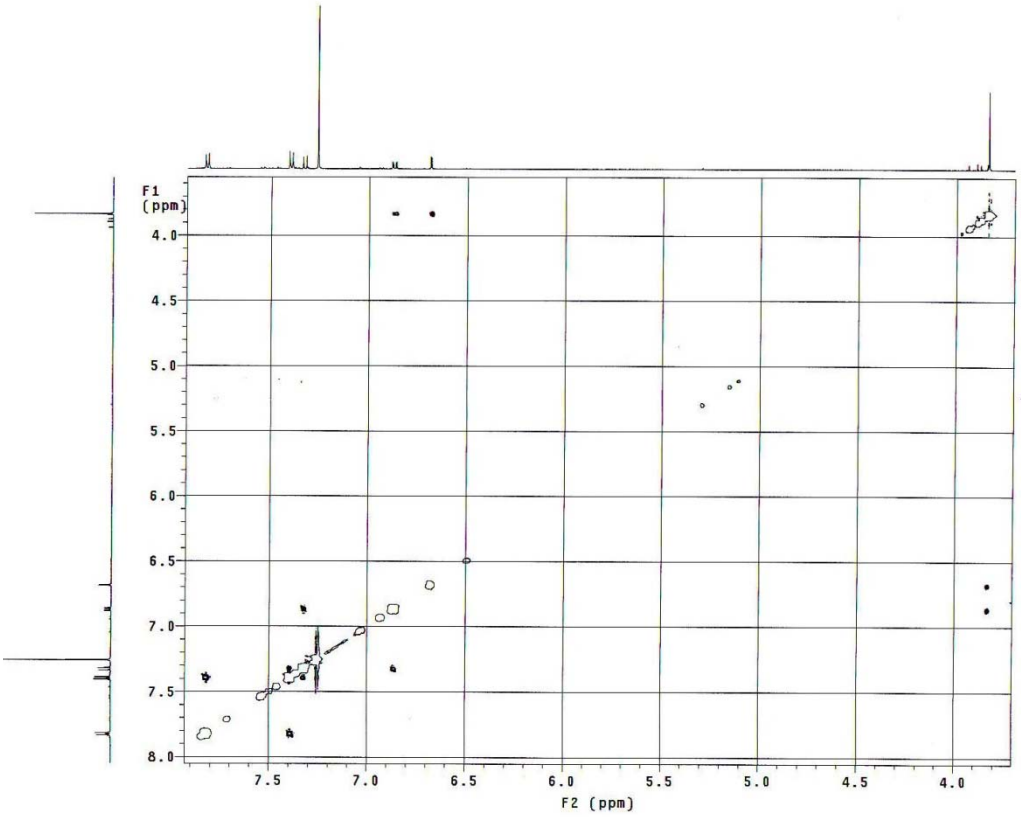

OH
MeO
B
O
O
Me
Me
Me
Me
10
9
8
7
6
5
4
3
2
1
ppm
180
160
140
120
100
80
60
40
20
ppm

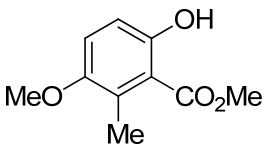

F1
(ppm)
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
0
F2 (ppm)


F1
(ppm)
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
F2 (ppm)

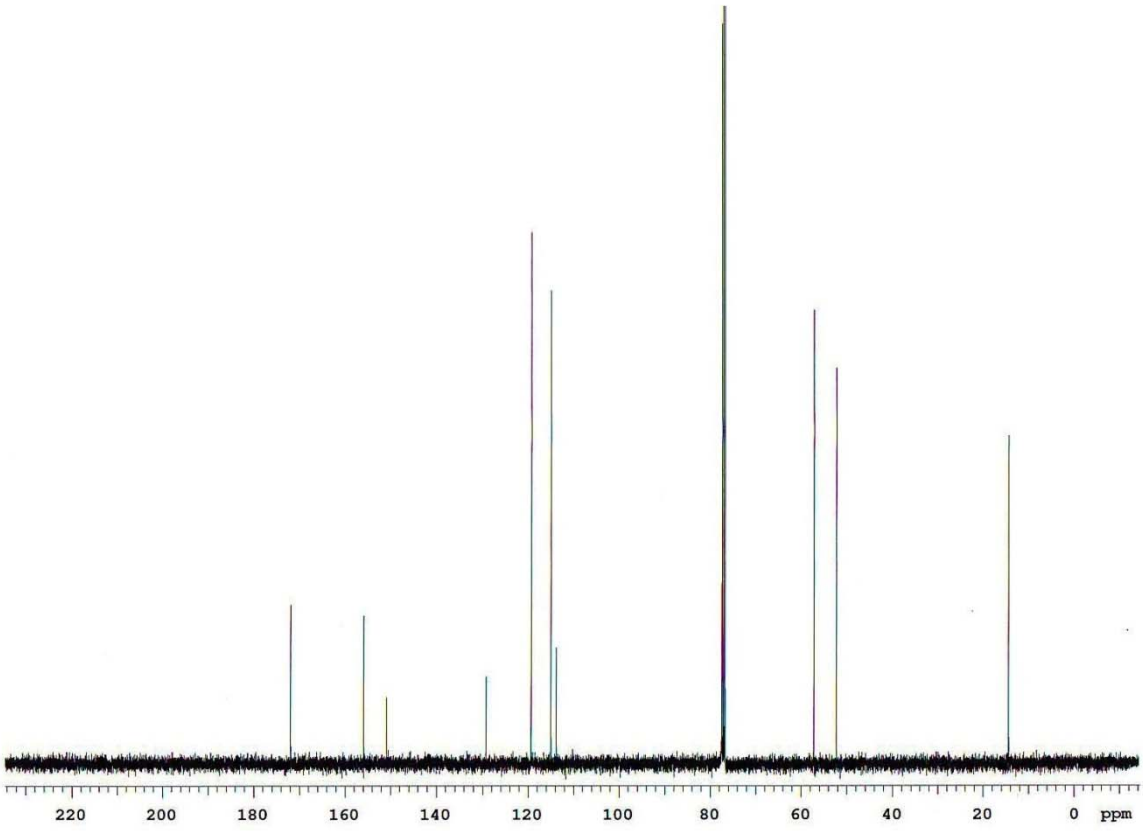

MeO
OAc
B
O
O
Me
Me
Me
Me
9
8
7
6
5
4
3
2
1
0
ppm
200
180
160
140
120
100
80
60
40
20
ppm

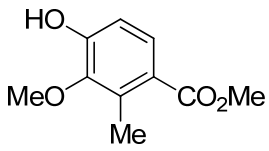

F1
(ppm)
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
0
F2 (ppm)

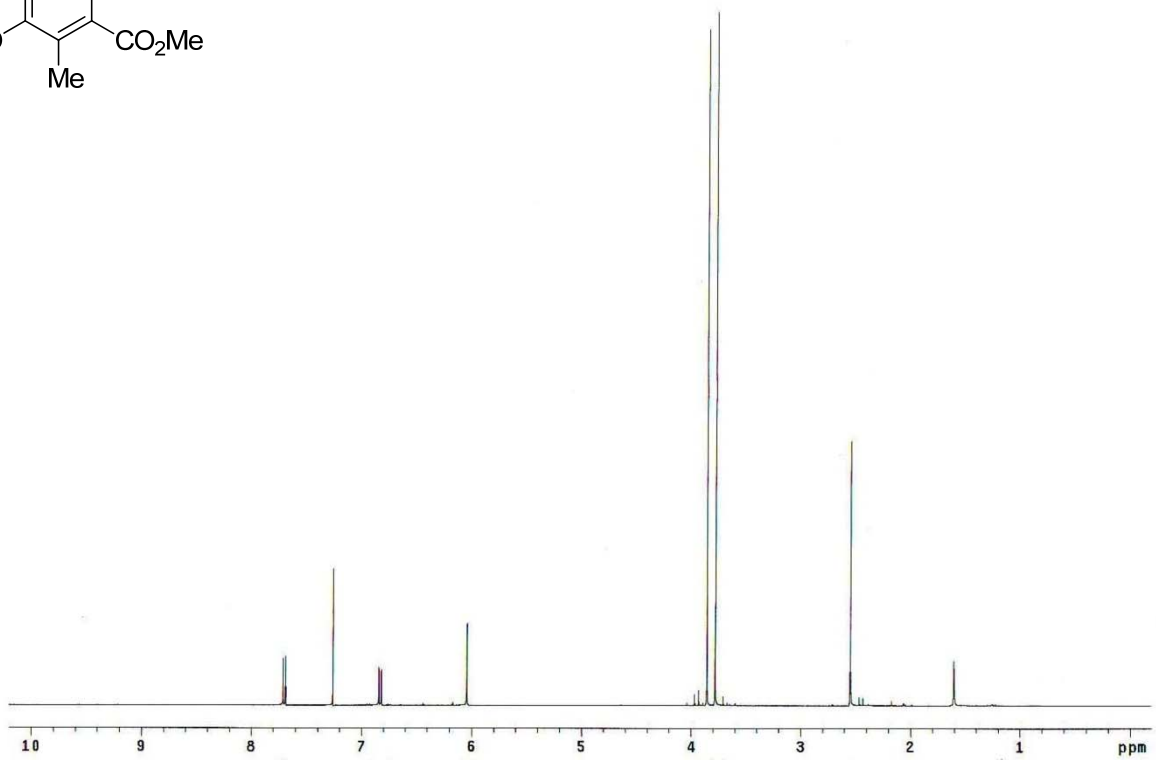

F1
(ppm)
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
F2 (ppm)

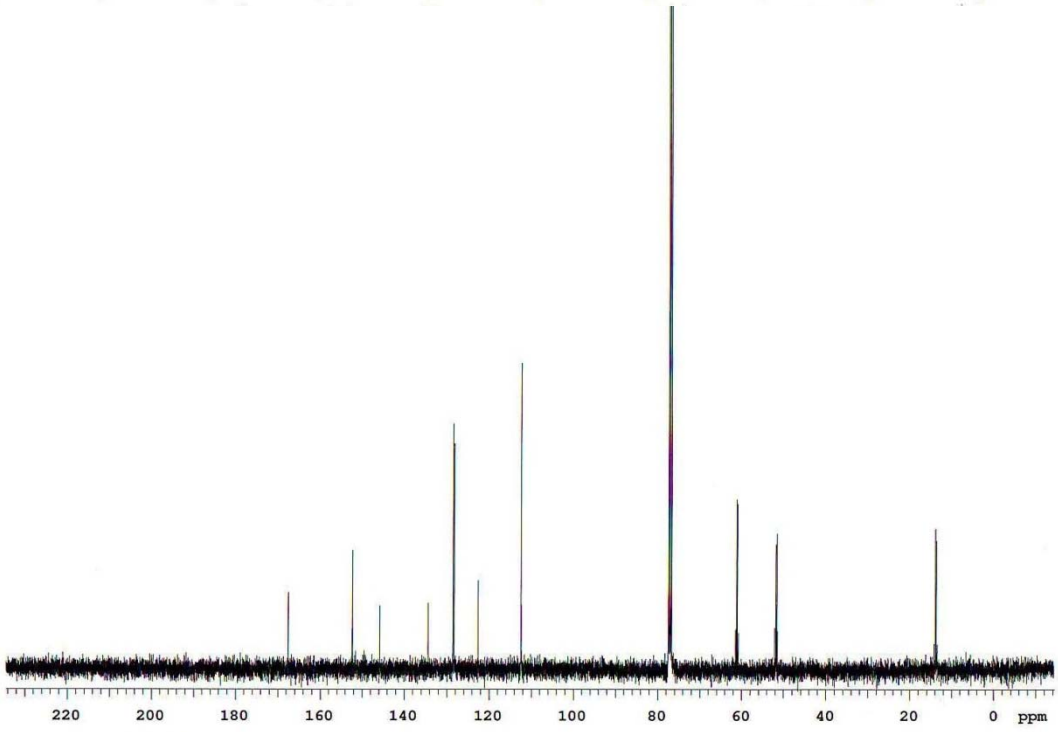

OH
MeO
CO2Me
Me

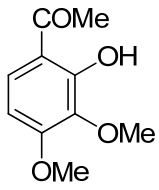
11
10
9
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

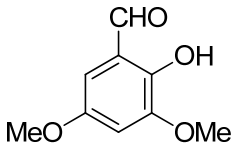

HO
MeO
CO2Me
Me


10
9
8
7
6
5
4
3
2
1
ppm

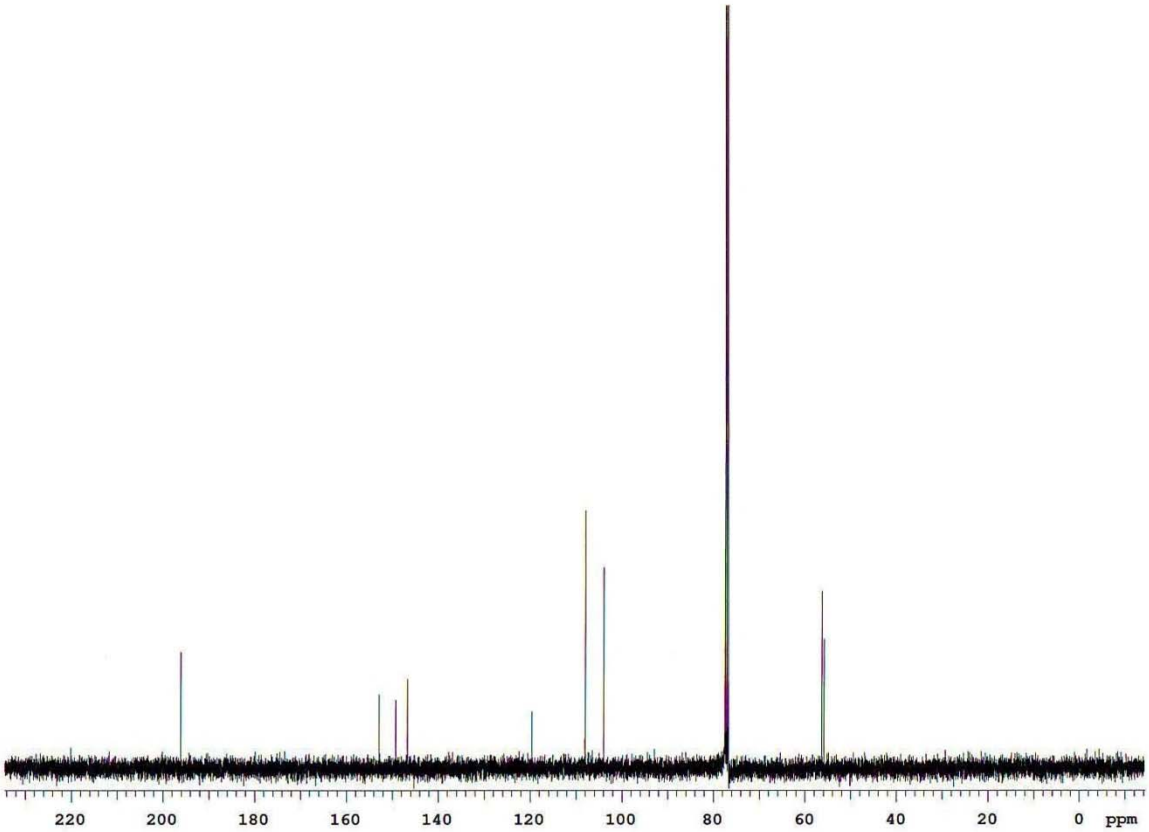

220
200
180
160
140
120
100
80
60
40
20
0
ppm


COMe
OH
OMe
OMe

12
11
10
9
8
7
6
5
4
3
2
1
ppm
200
180
160
140
120
100
80
60
40
20
ppm


CHO
OH
MeO
OMe

12
10
8
6
4
2
-0
ppm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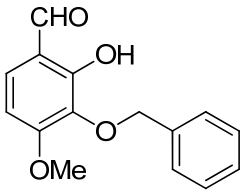
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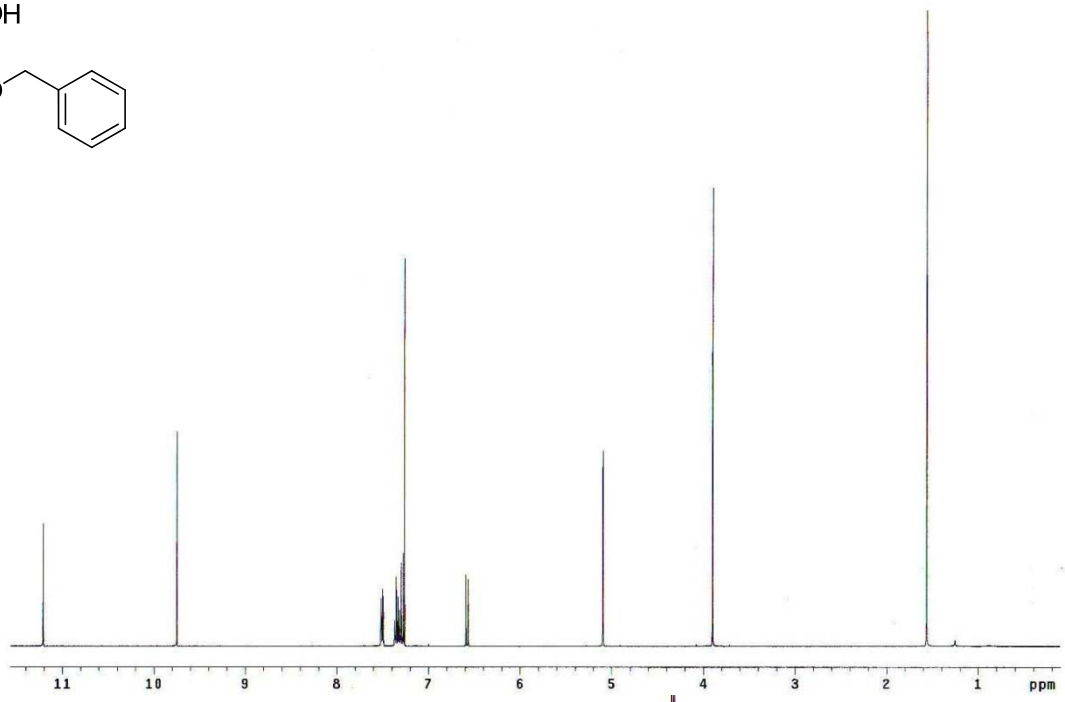
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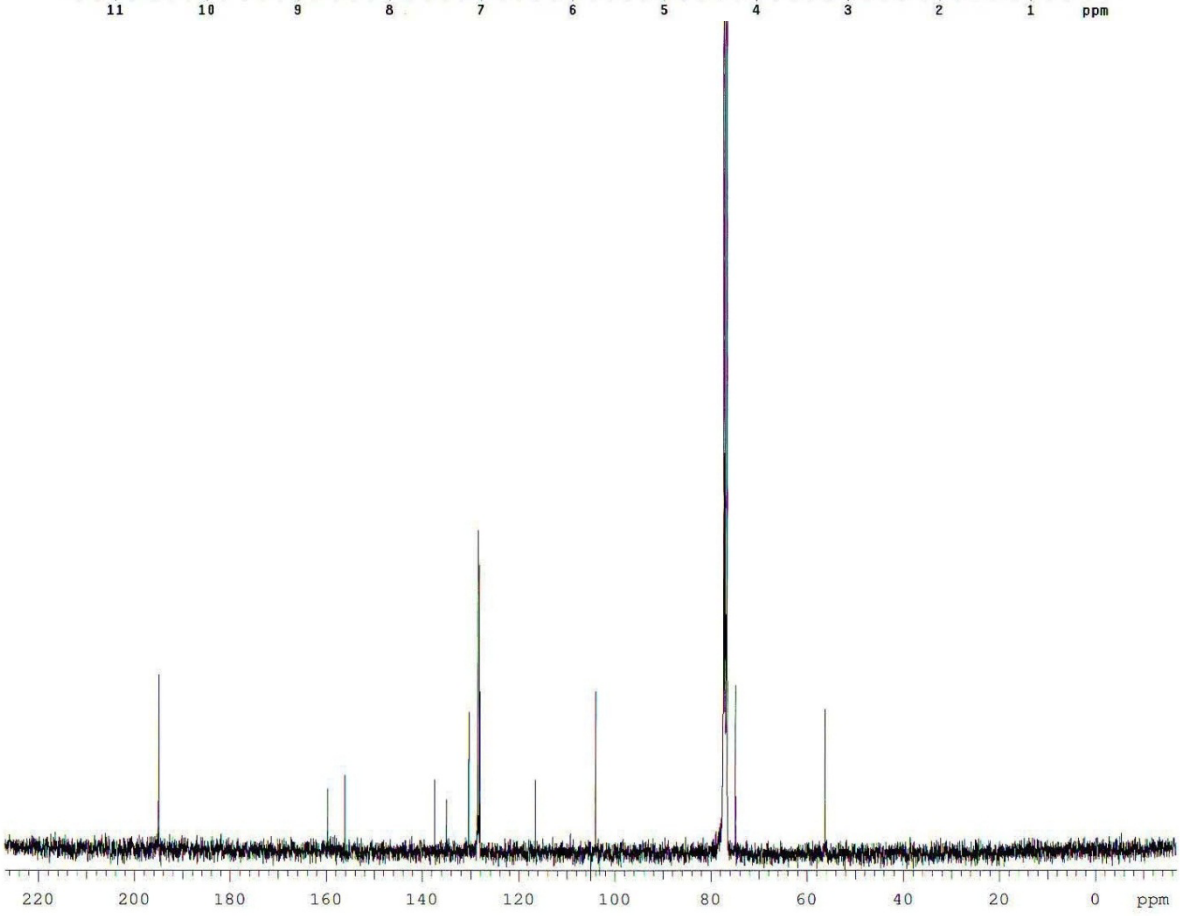
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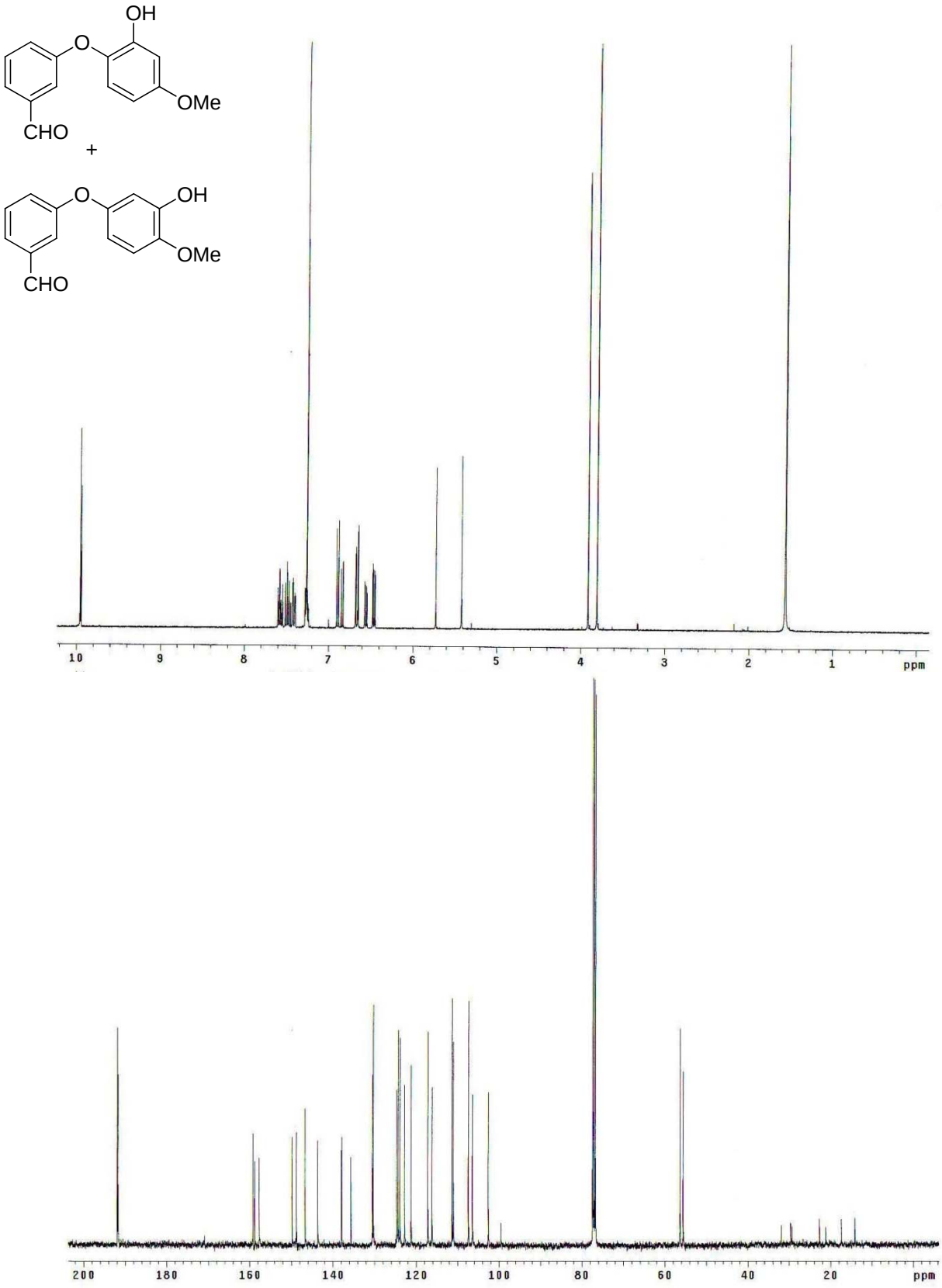
OH
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OMe
CHO
+
O
OH
OMe
CHO
10
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4
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2
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ppm
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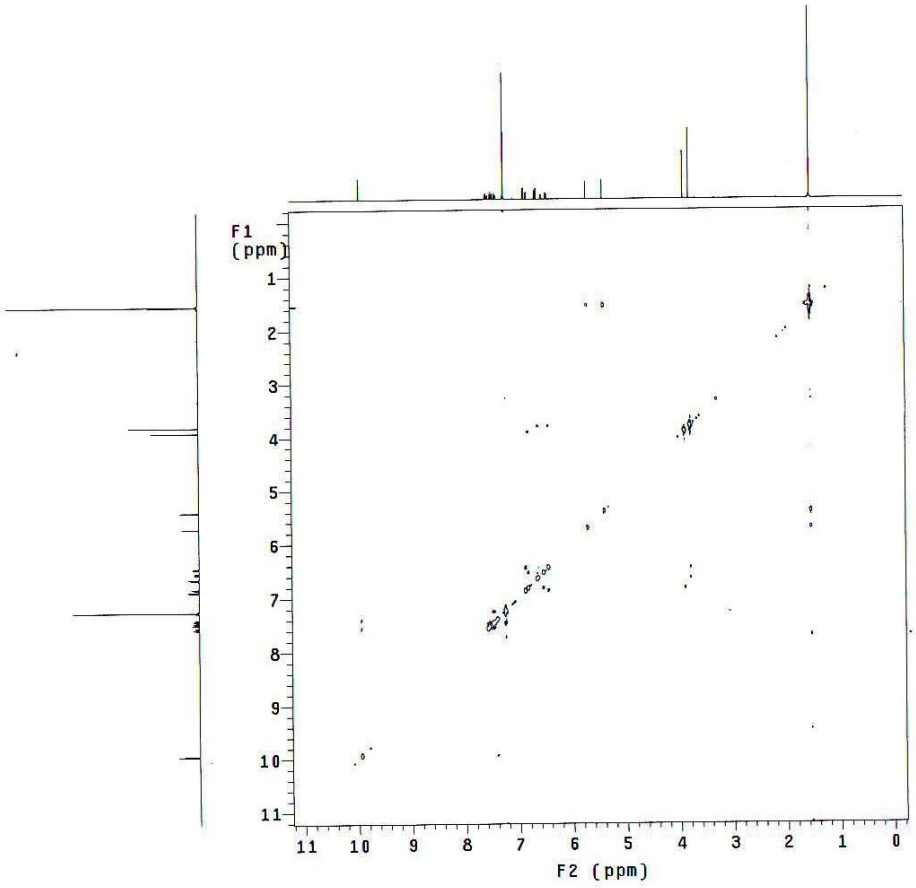
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(ppm)
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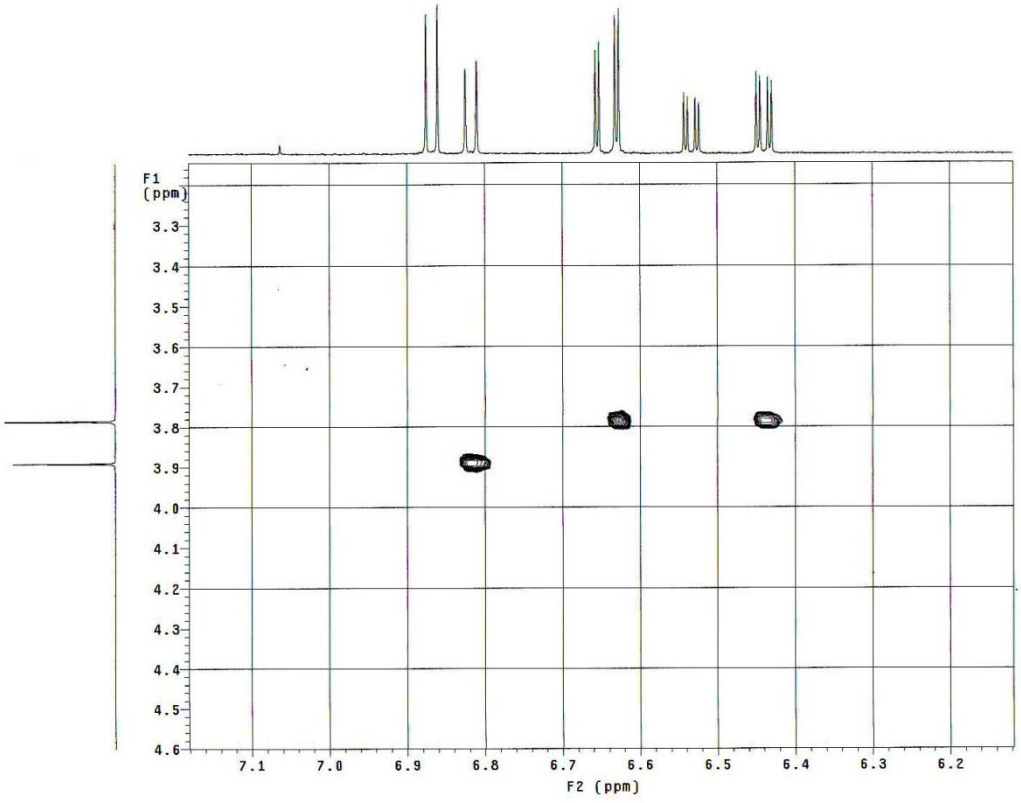
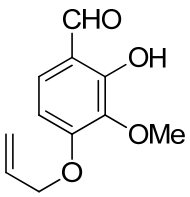
10
11
11 10 9 8 7 6 5 4 3 2 1 0
F2 (ppm)


F1
(ppm)
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4.0
4.1
4.2
4.3
4.4
4.5
4.6
7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2
F2 (ppm)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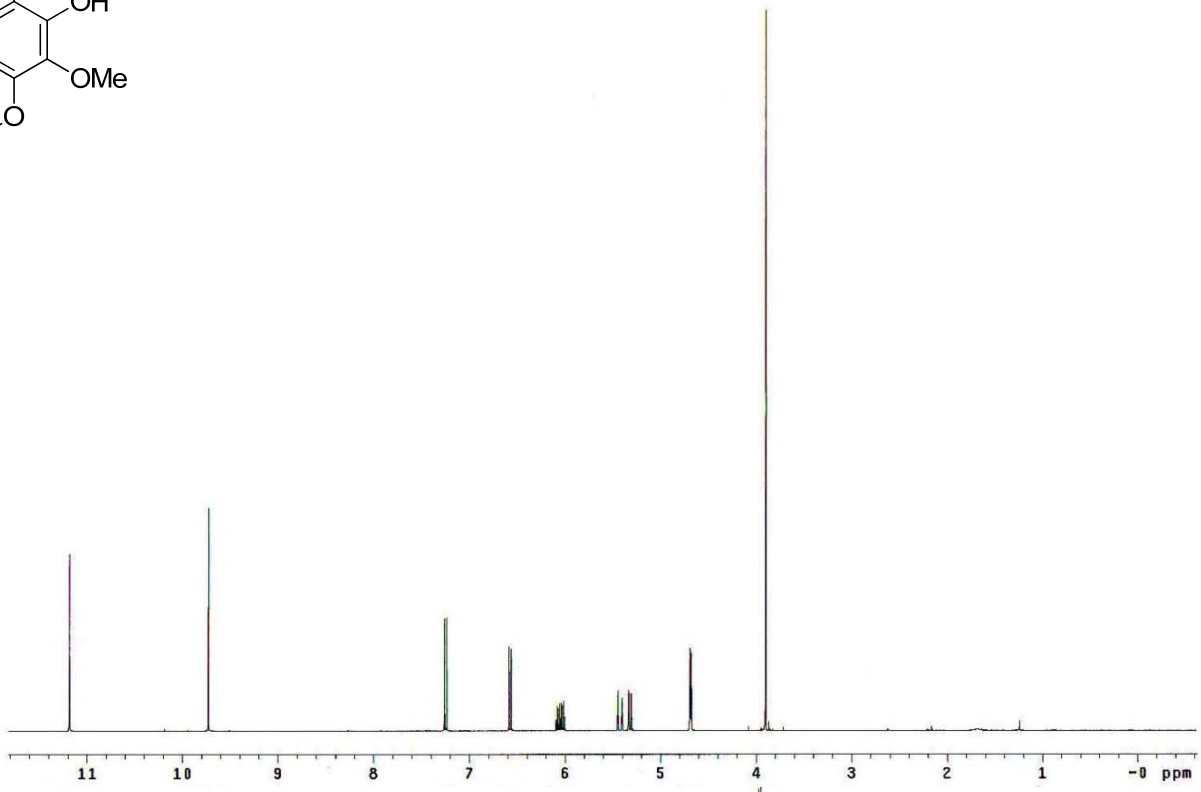
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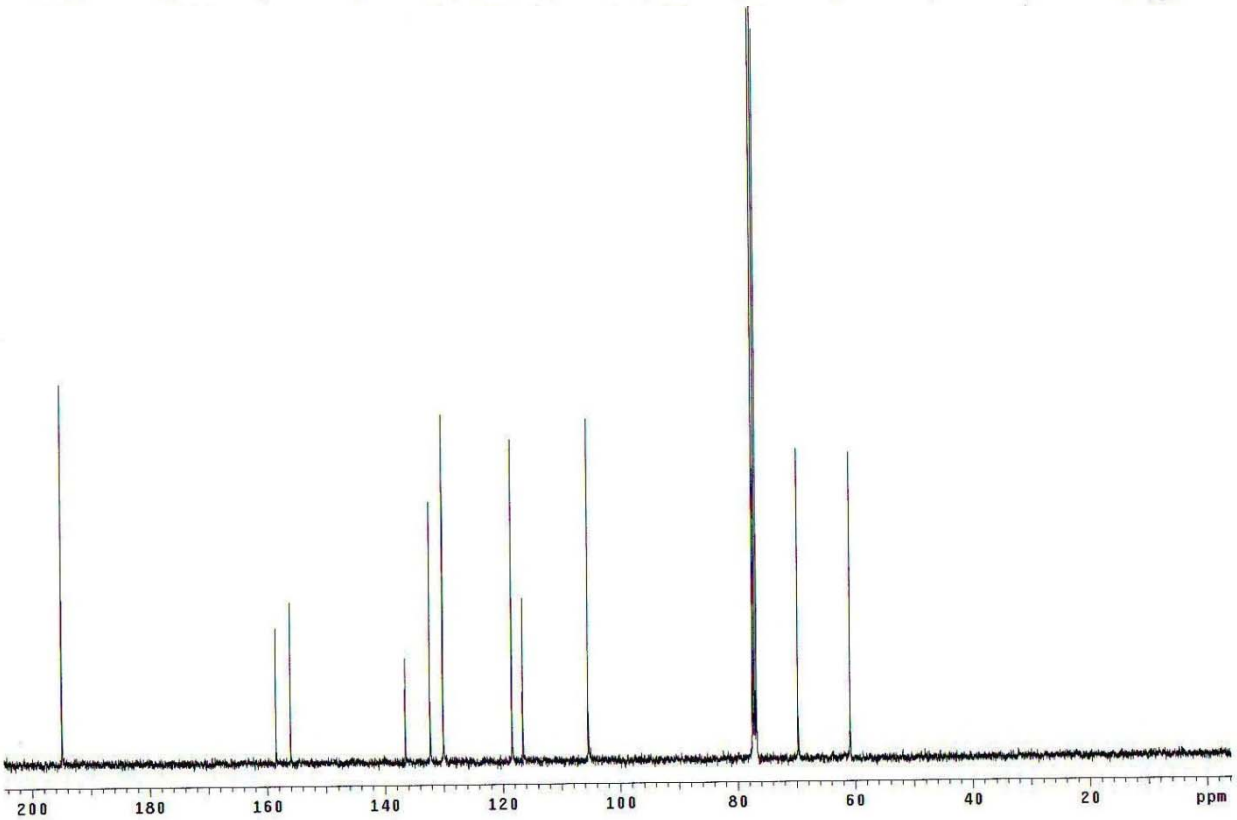
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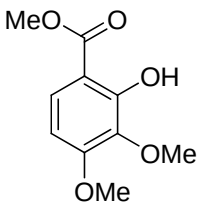
MeO
O
OH
OMe
OMe

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4
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-0
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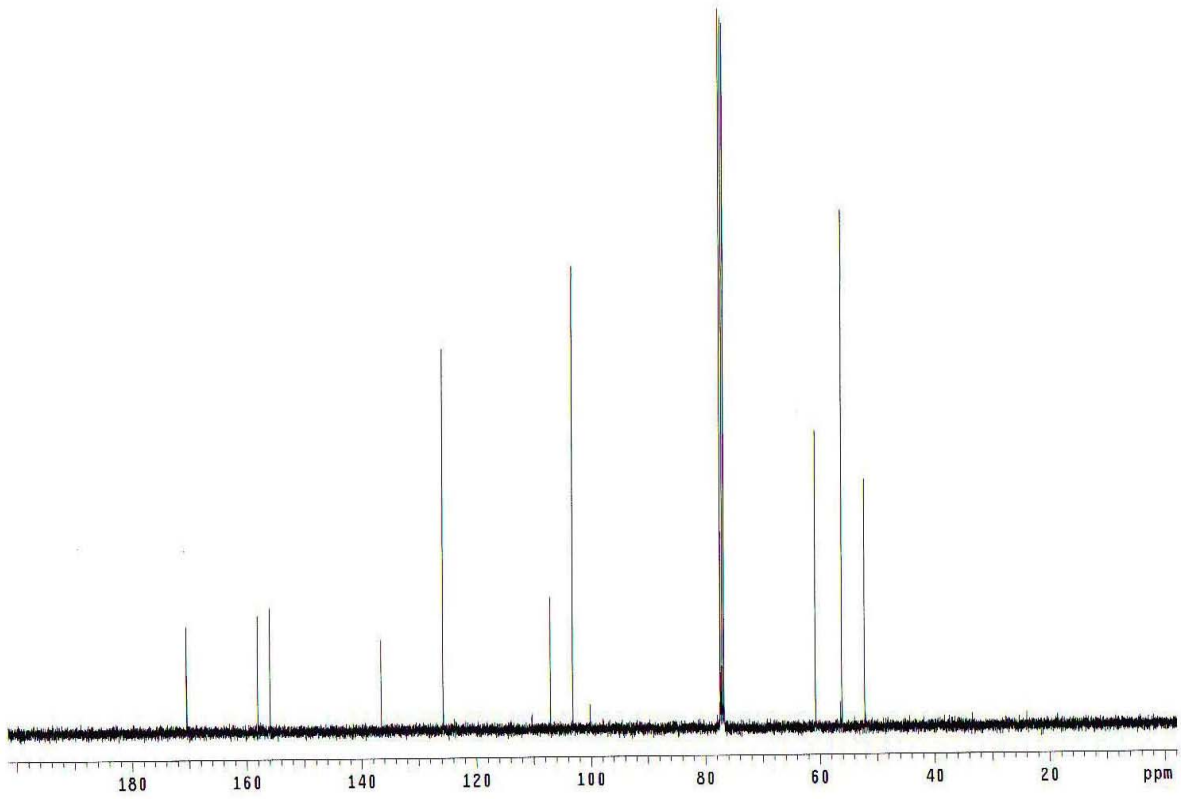
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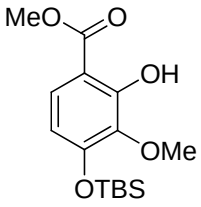
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OMe
OTBS

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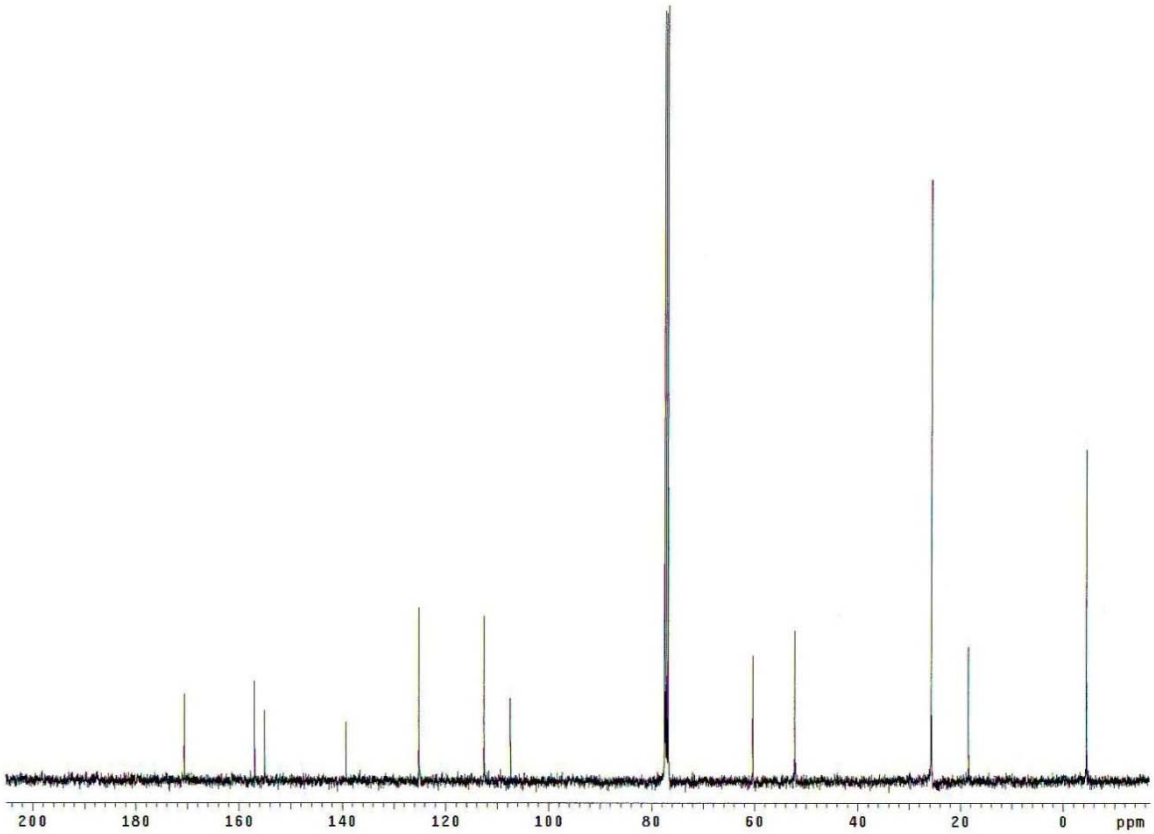
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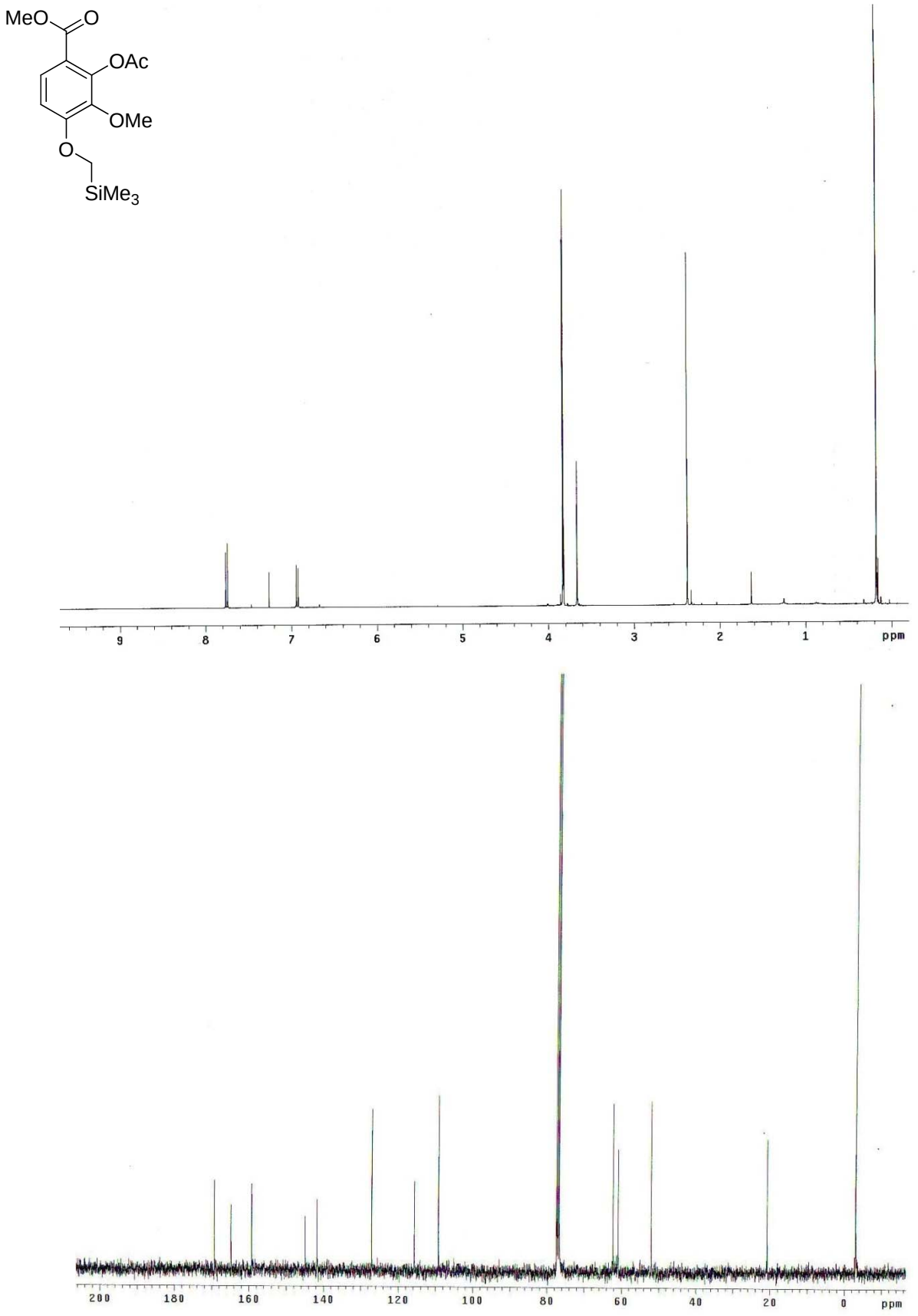
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OMe
O
SiMe3
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3
2
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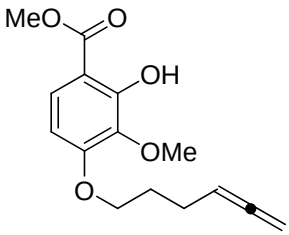
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OH
OMe
O

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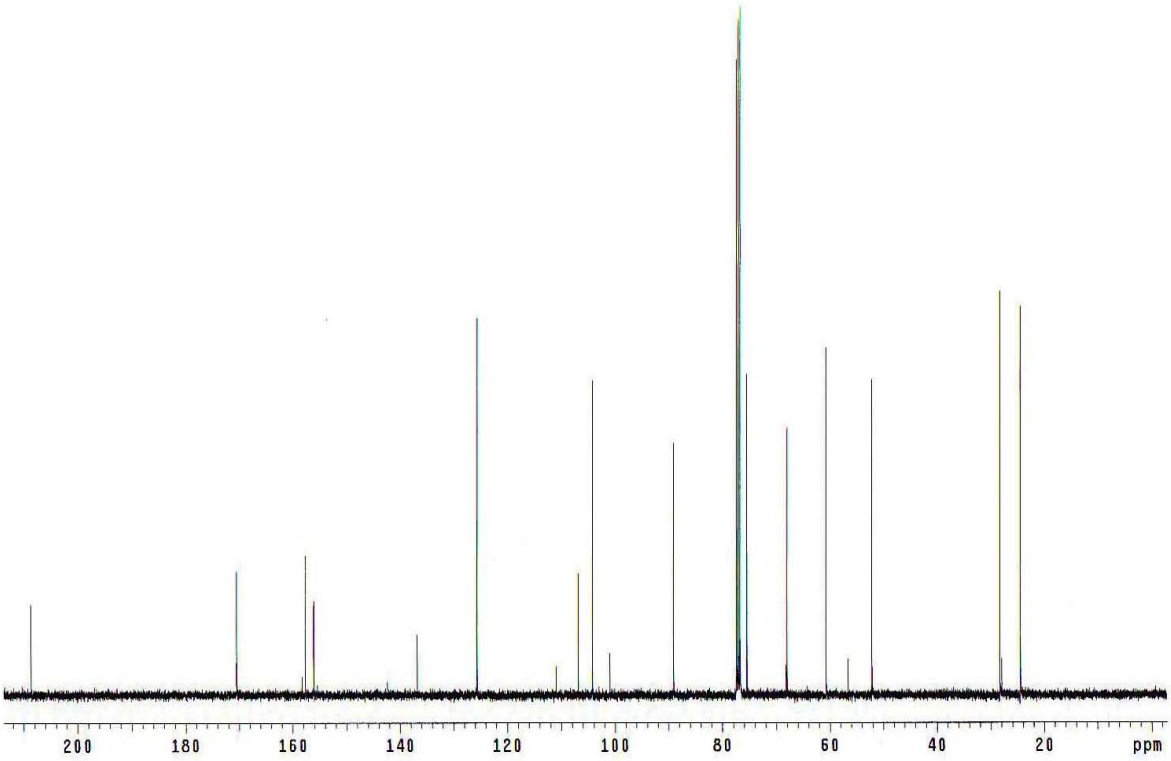
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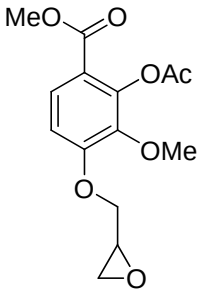
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OAc
OMe
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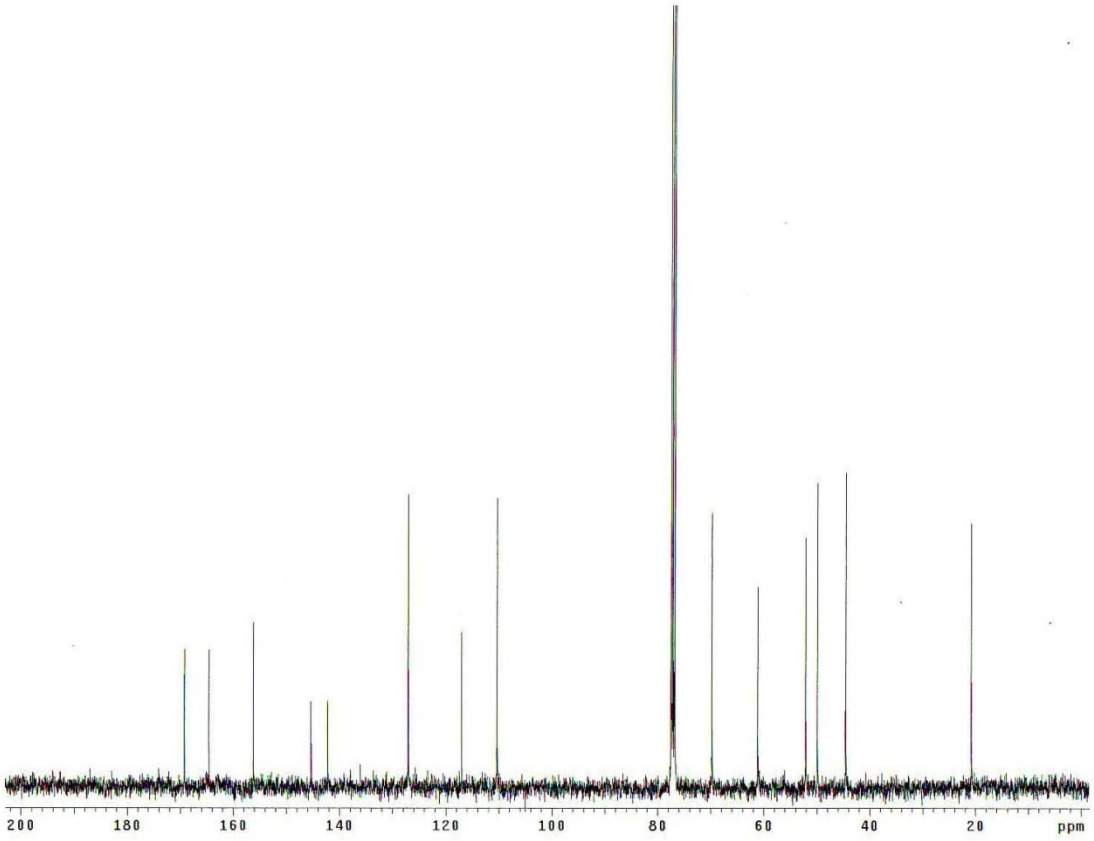
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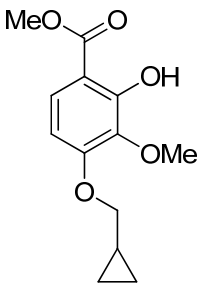
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OMe
O

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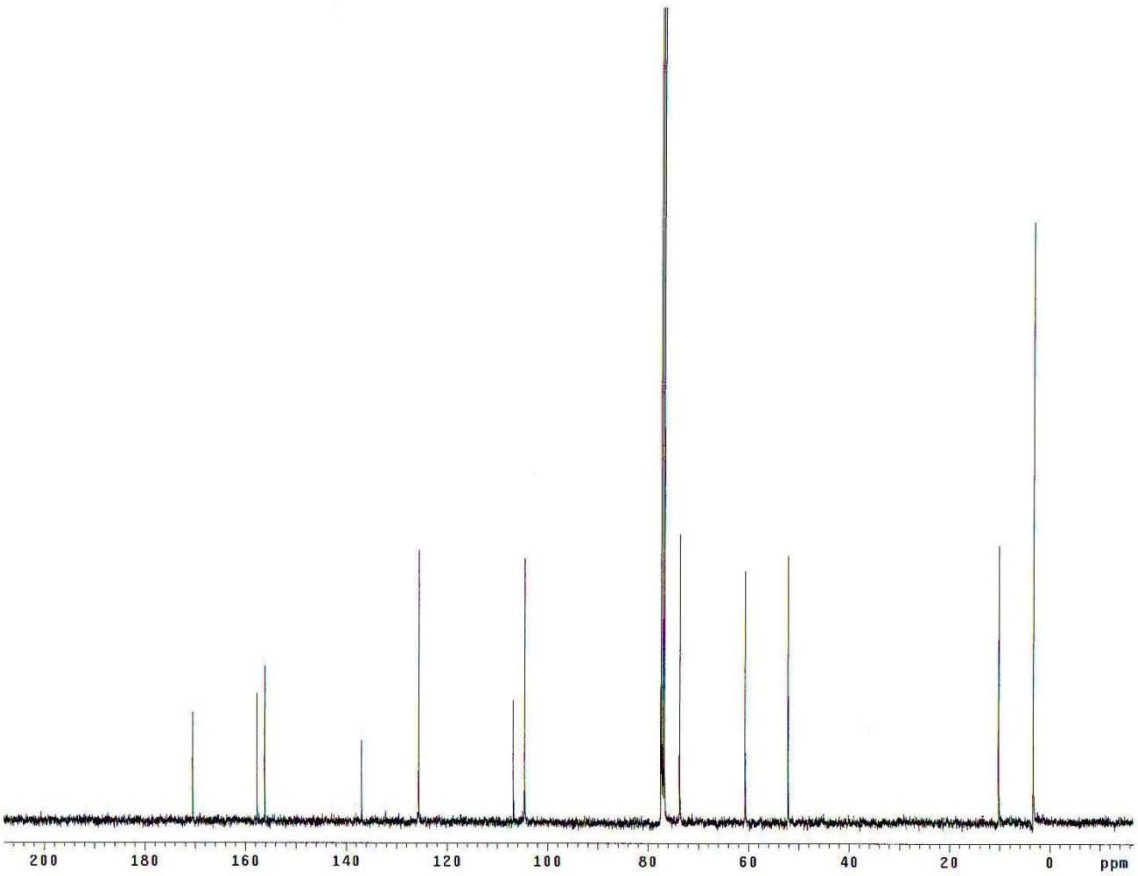
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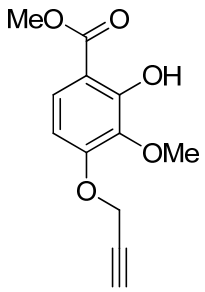
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OH
OMe
O

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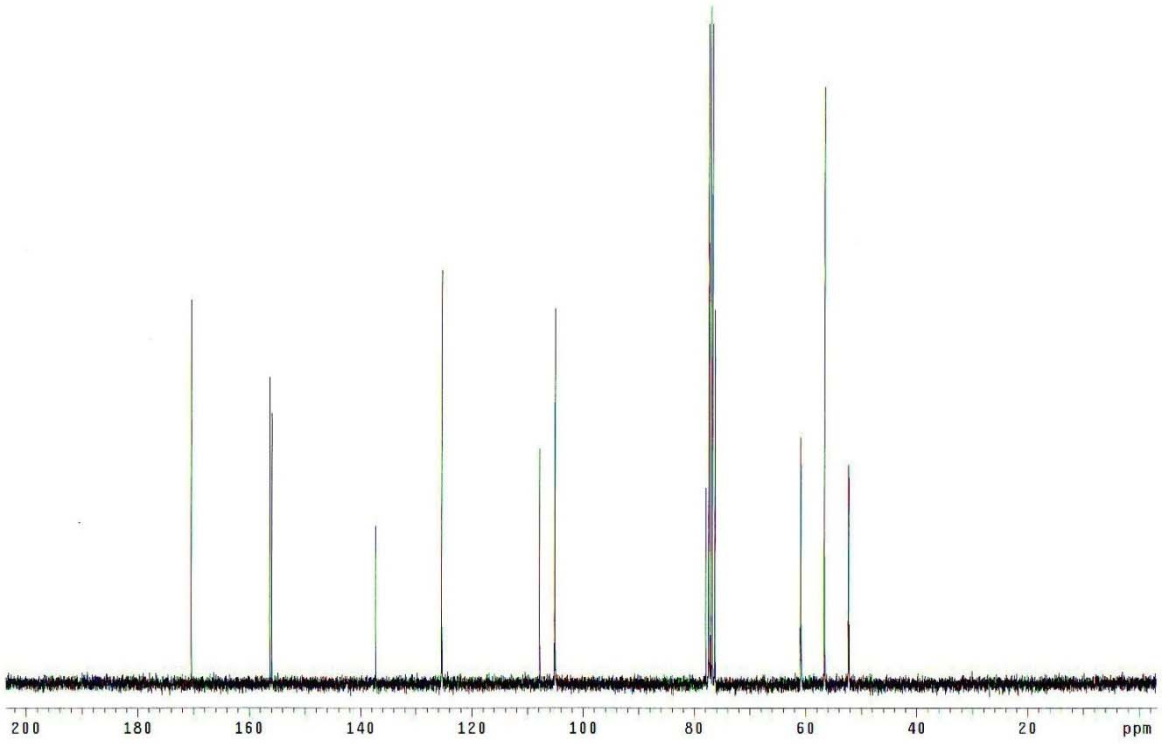
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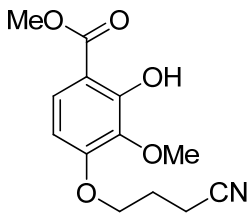
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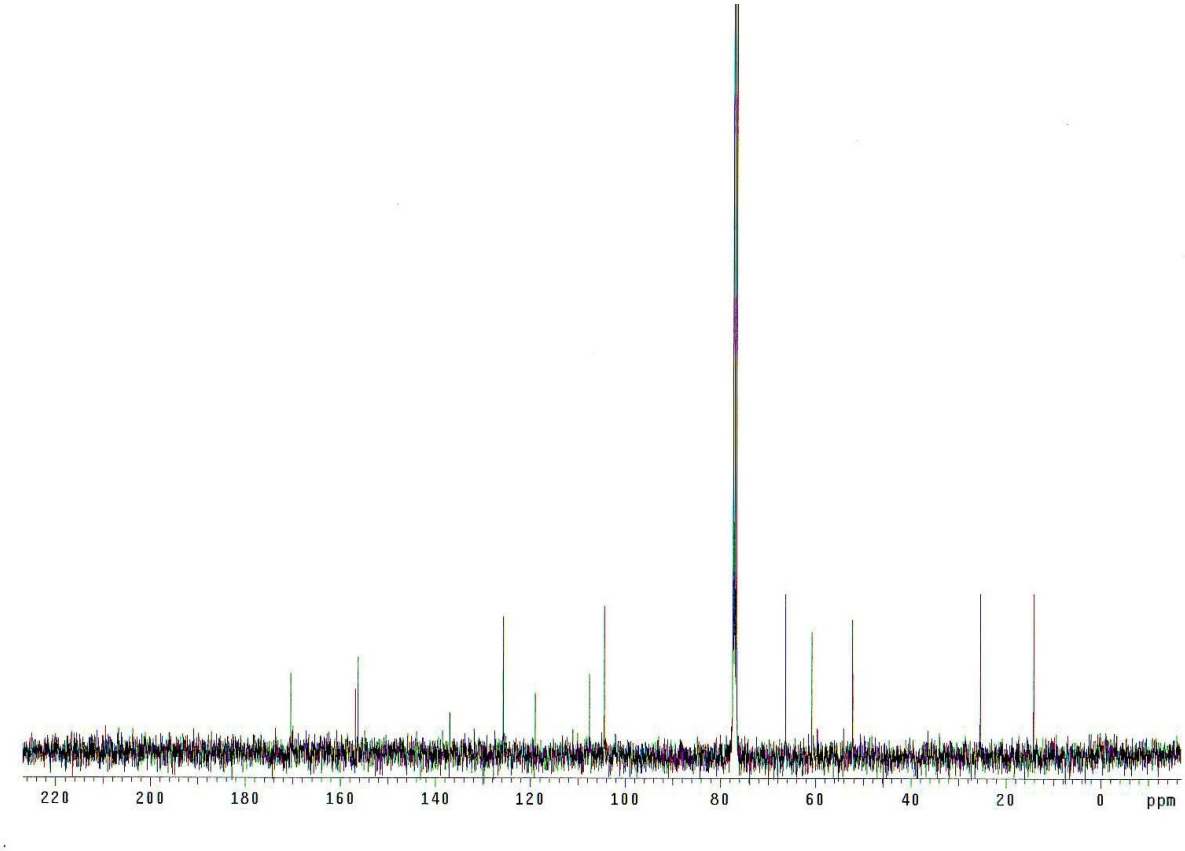
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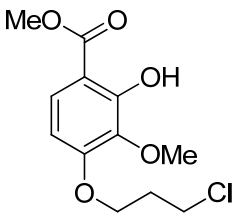
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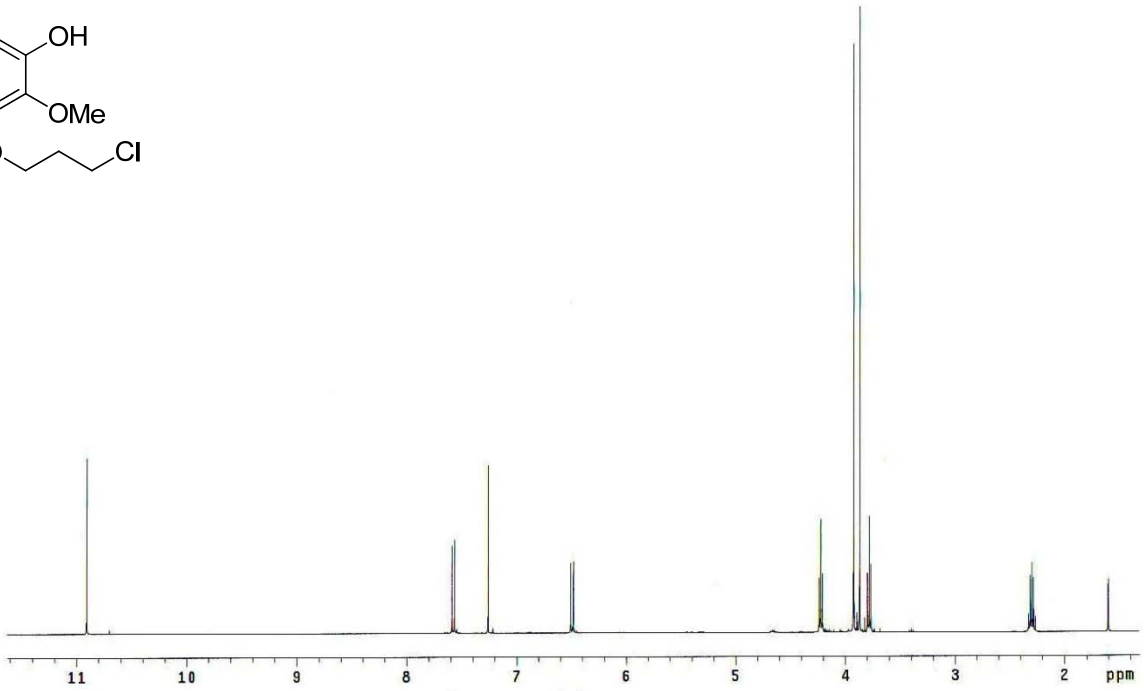
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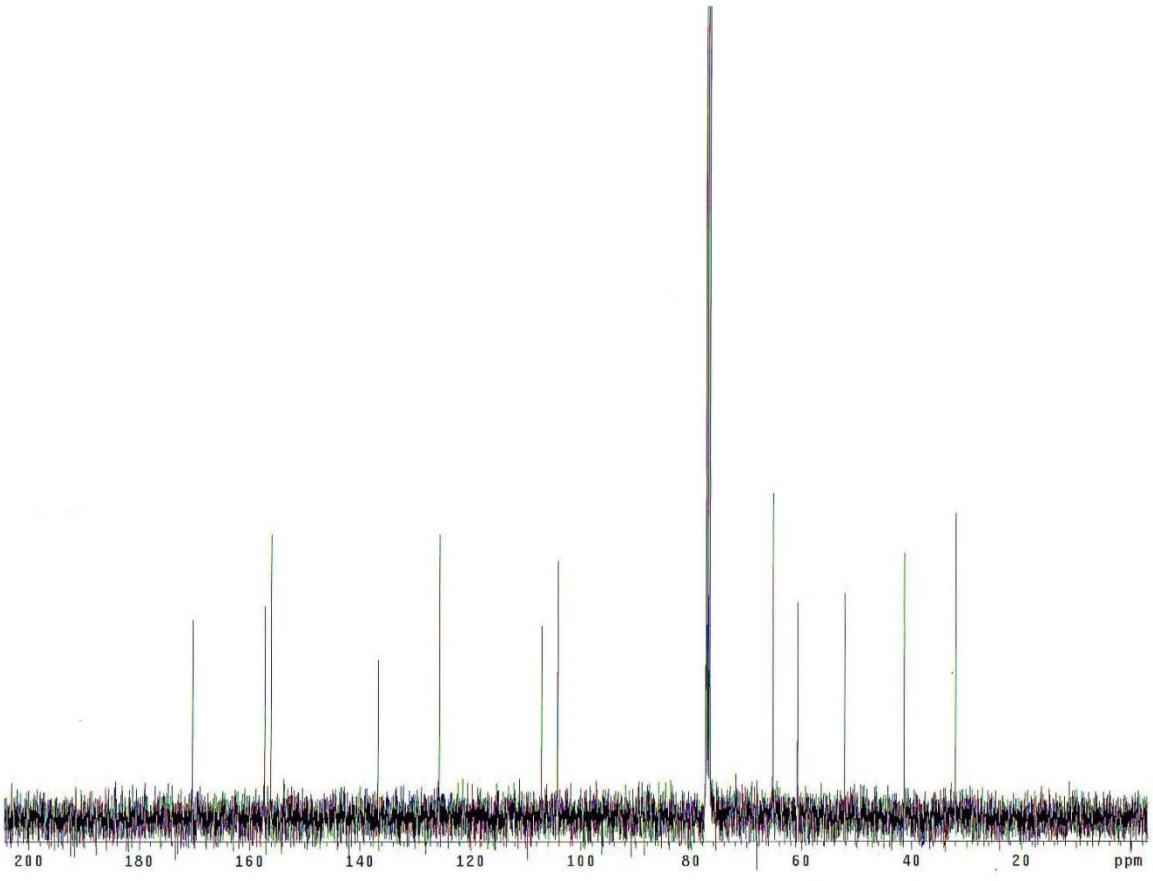
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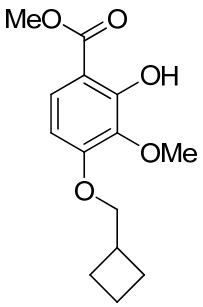
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OH
OMe
O

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5
4
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2
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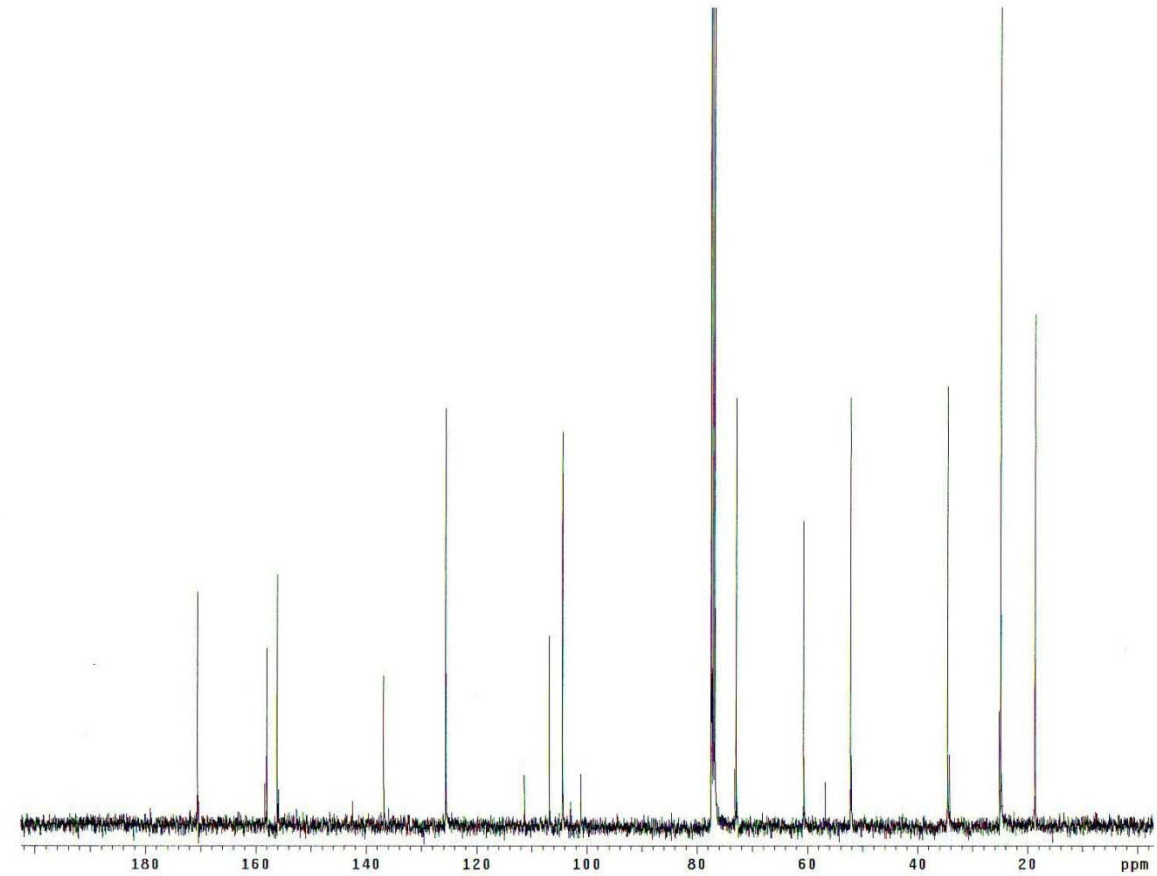
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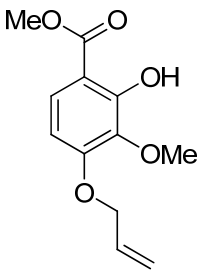
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OH
OMe
O

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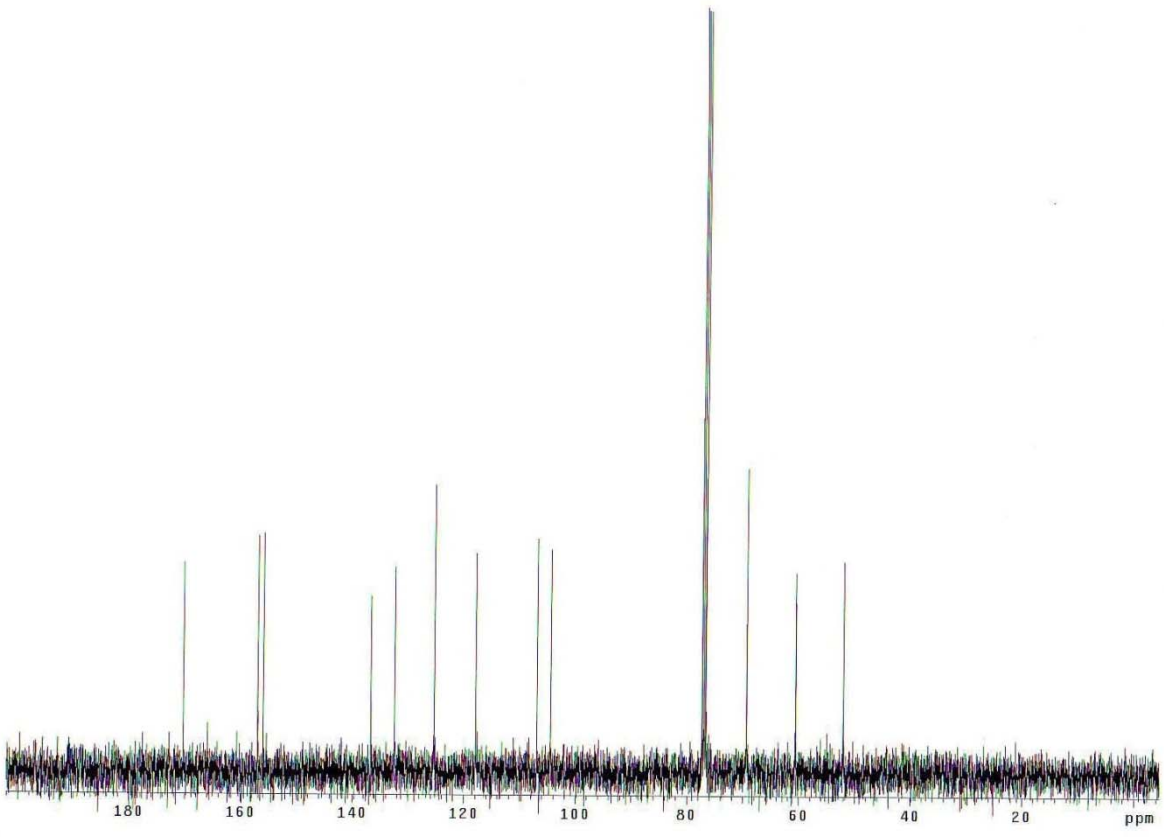
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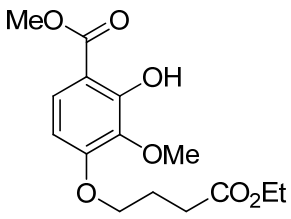
MeO
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OH
OMe
O
CO2Et

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5
4
3
2
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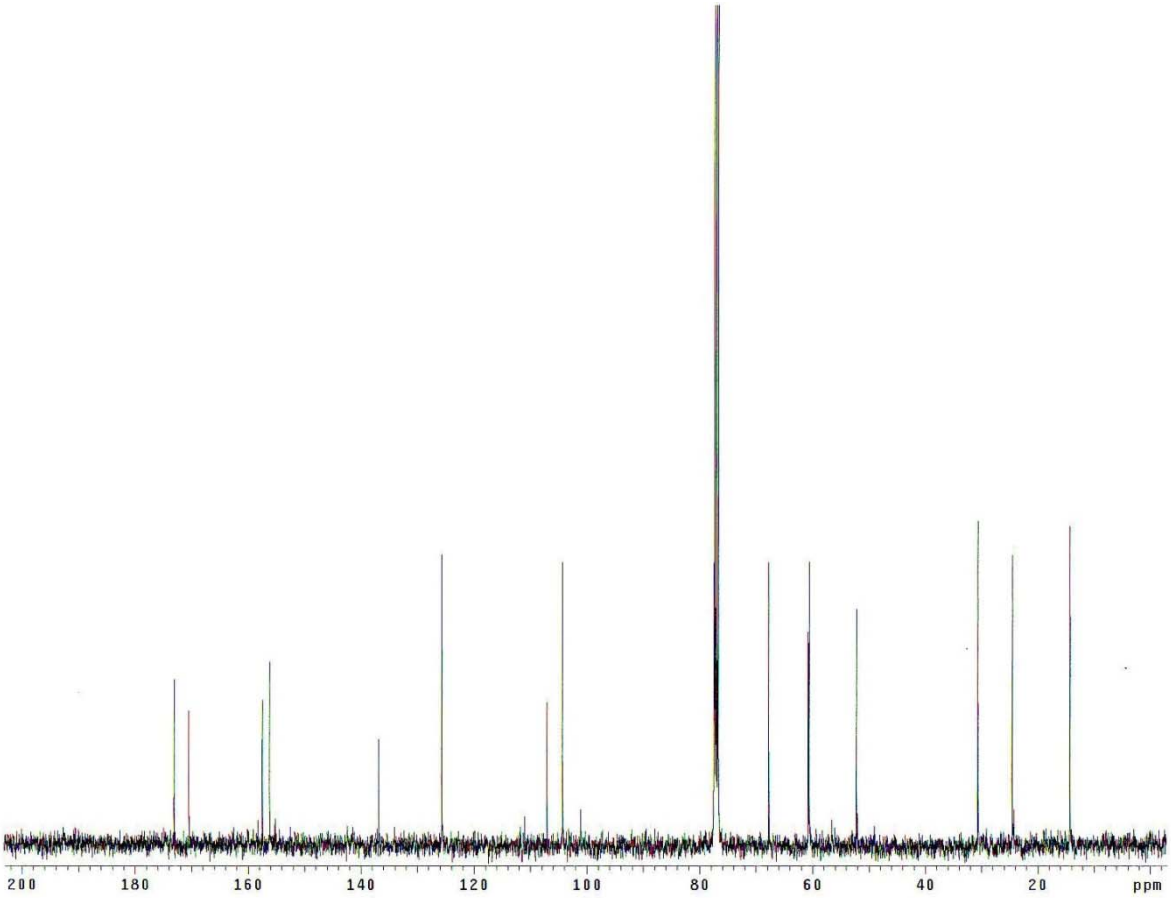
-0
ppm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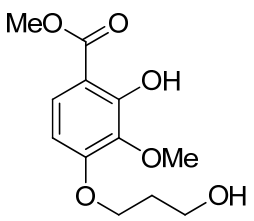
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OMe
O
OH

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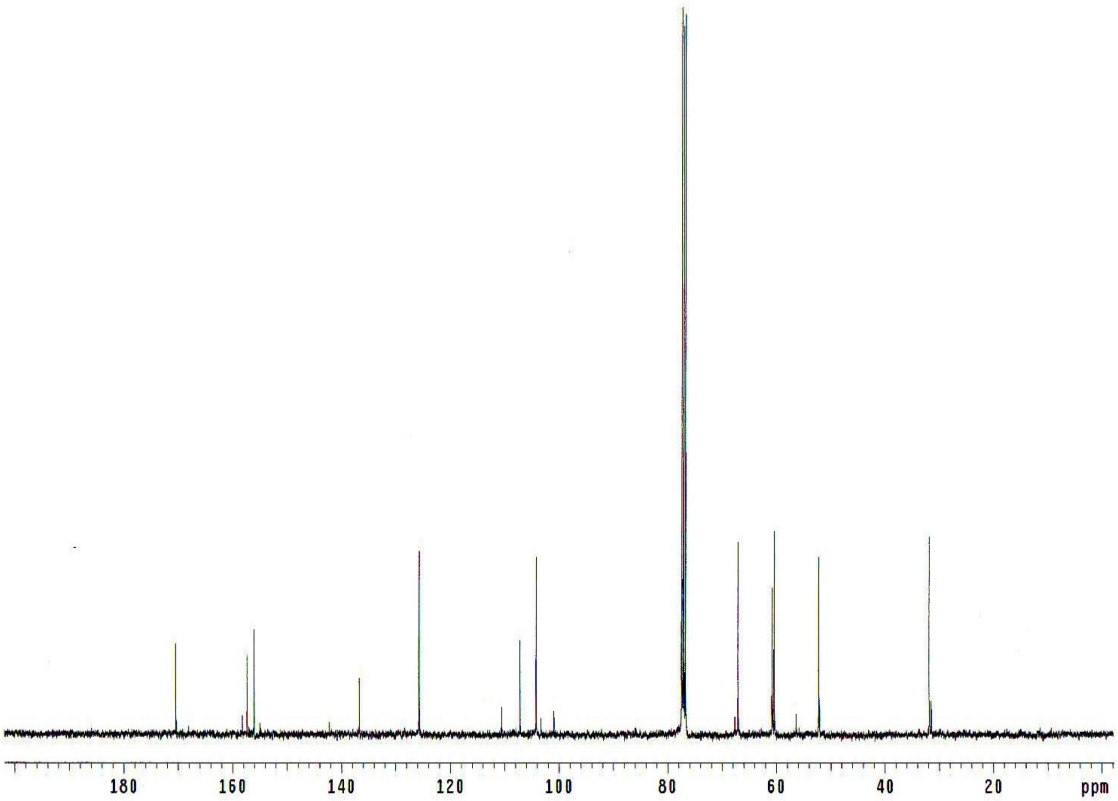
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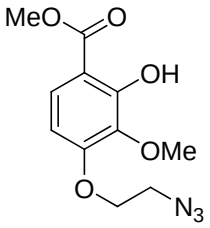
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OH
OMe
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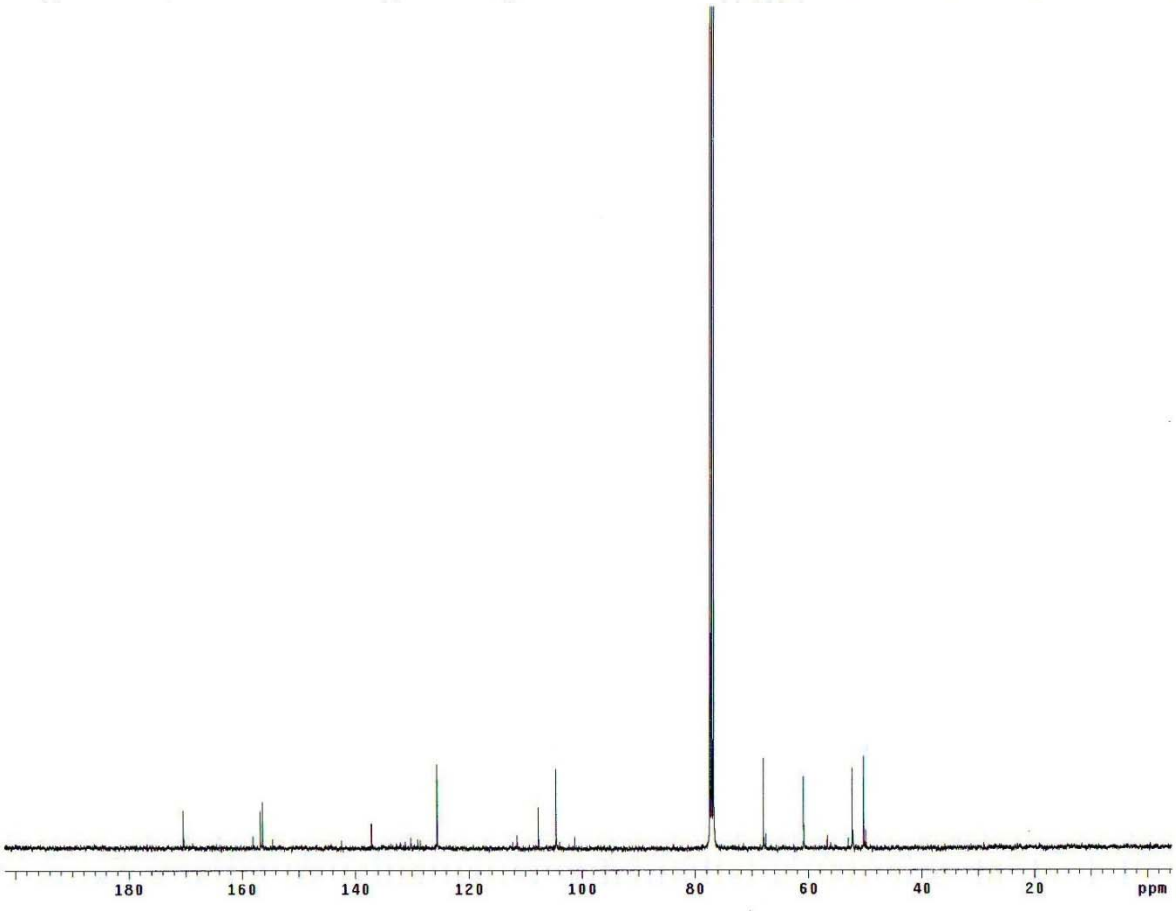
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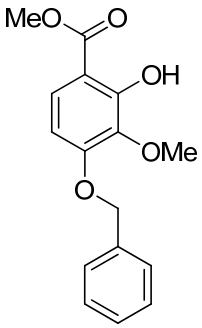
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OH
OMe
O

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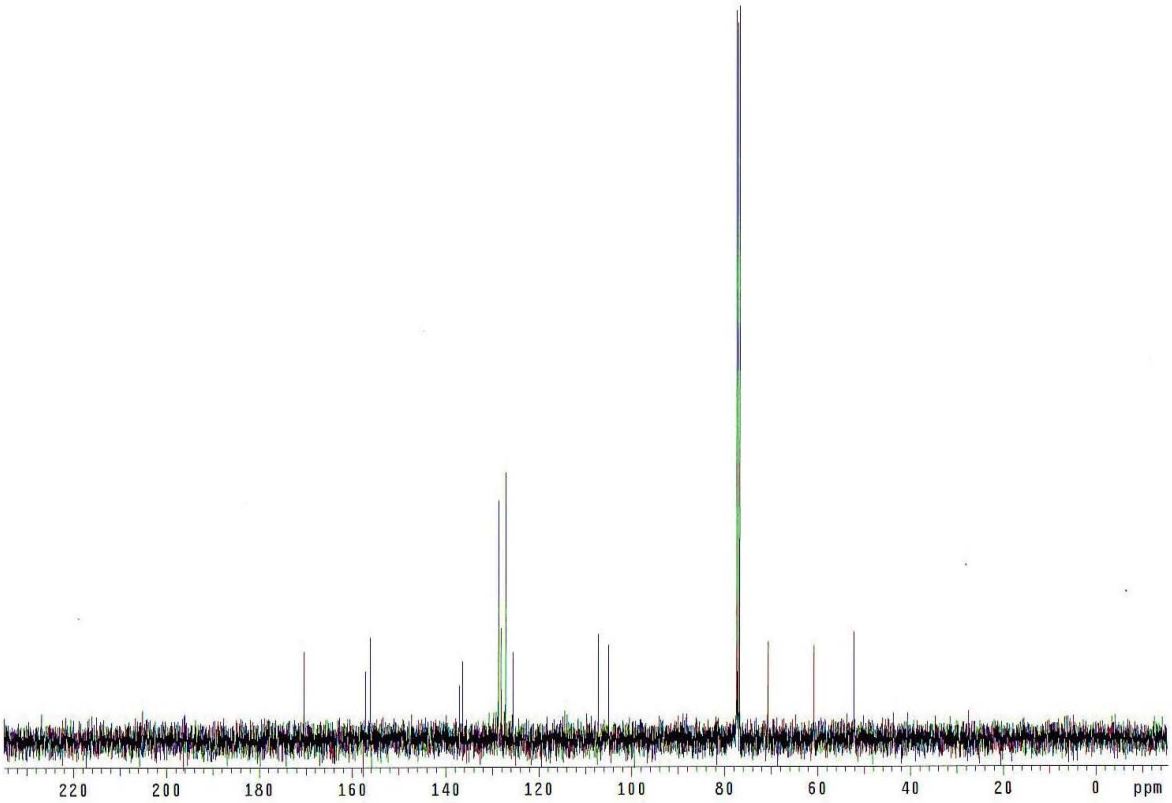
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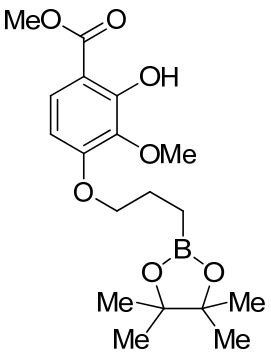
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O
OH
OMe
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B
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Me
Me
Me

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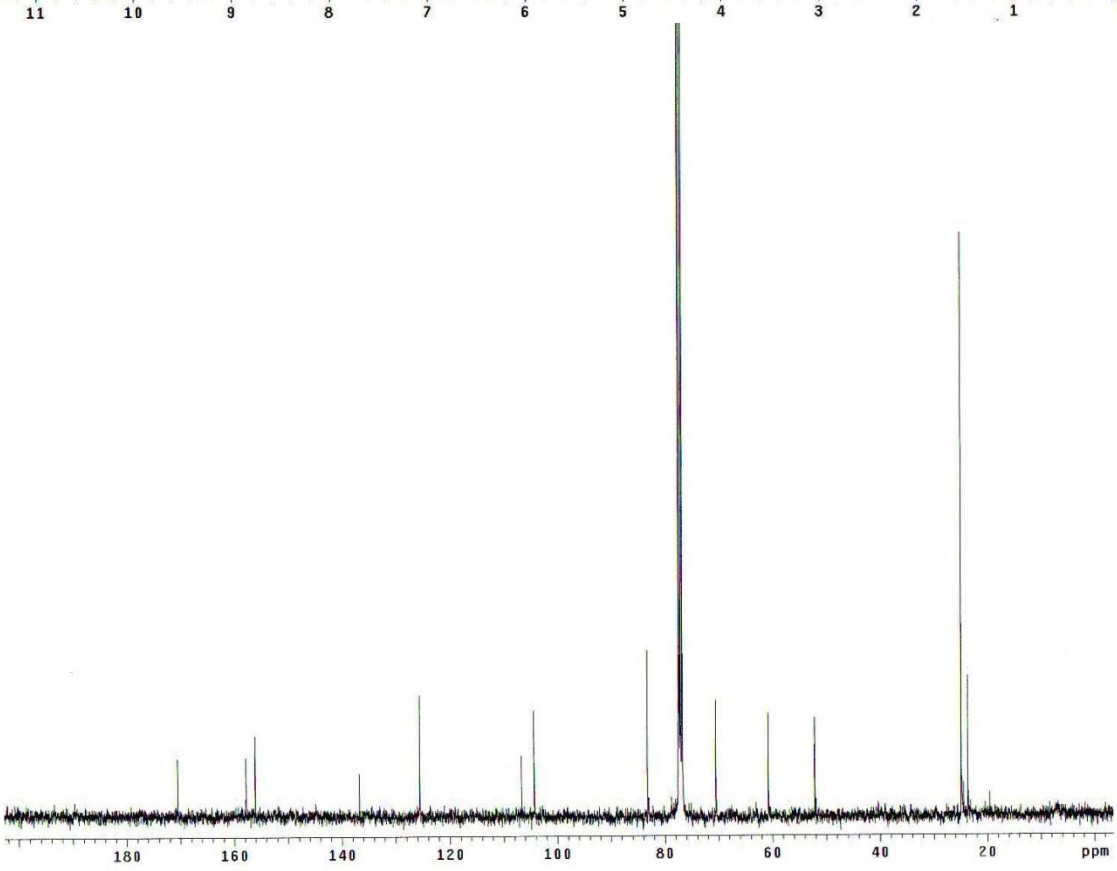
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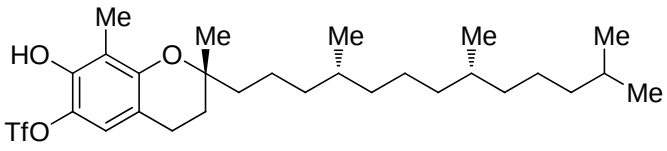
Me
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Me
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Me
Me
Me
Me
TfO

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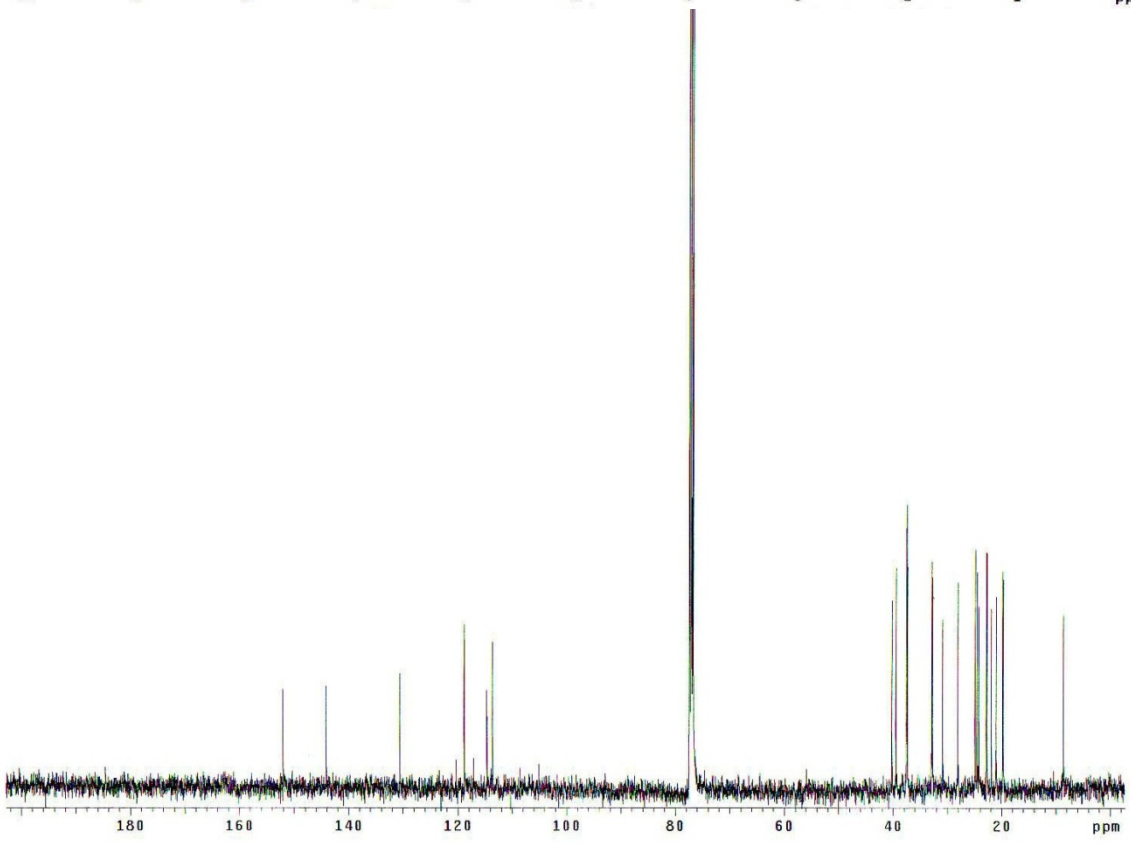
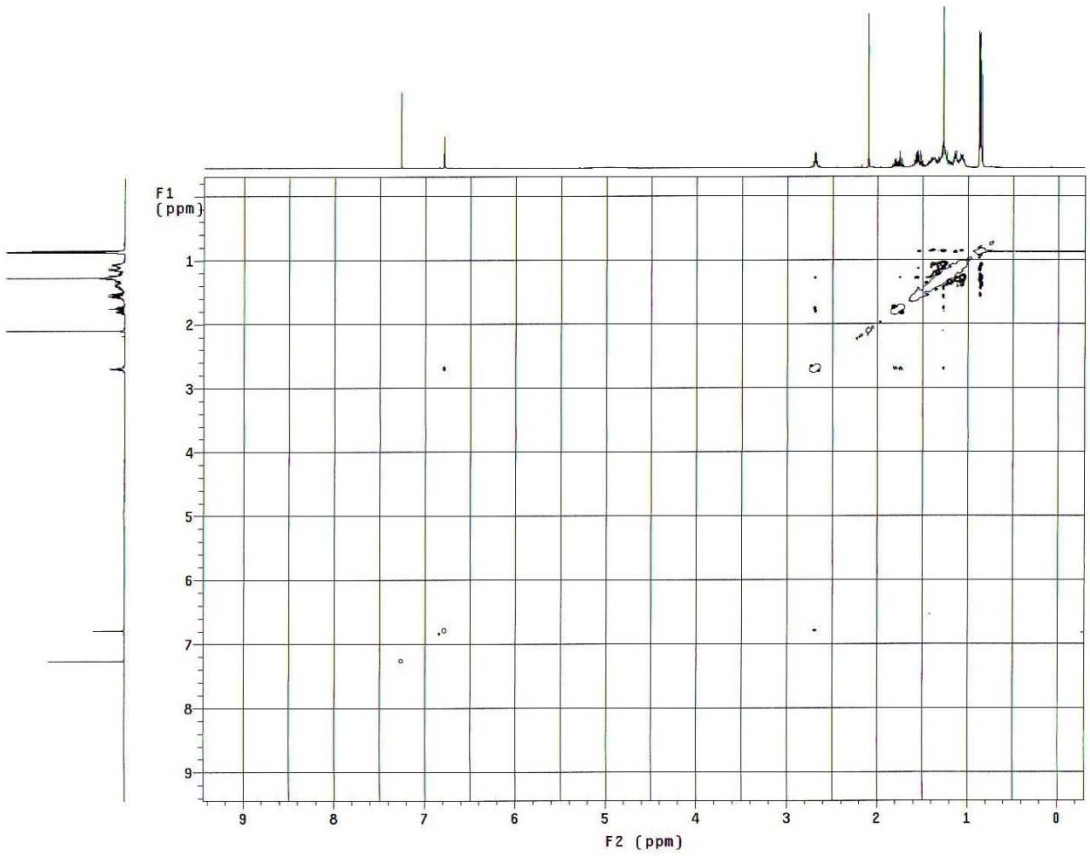
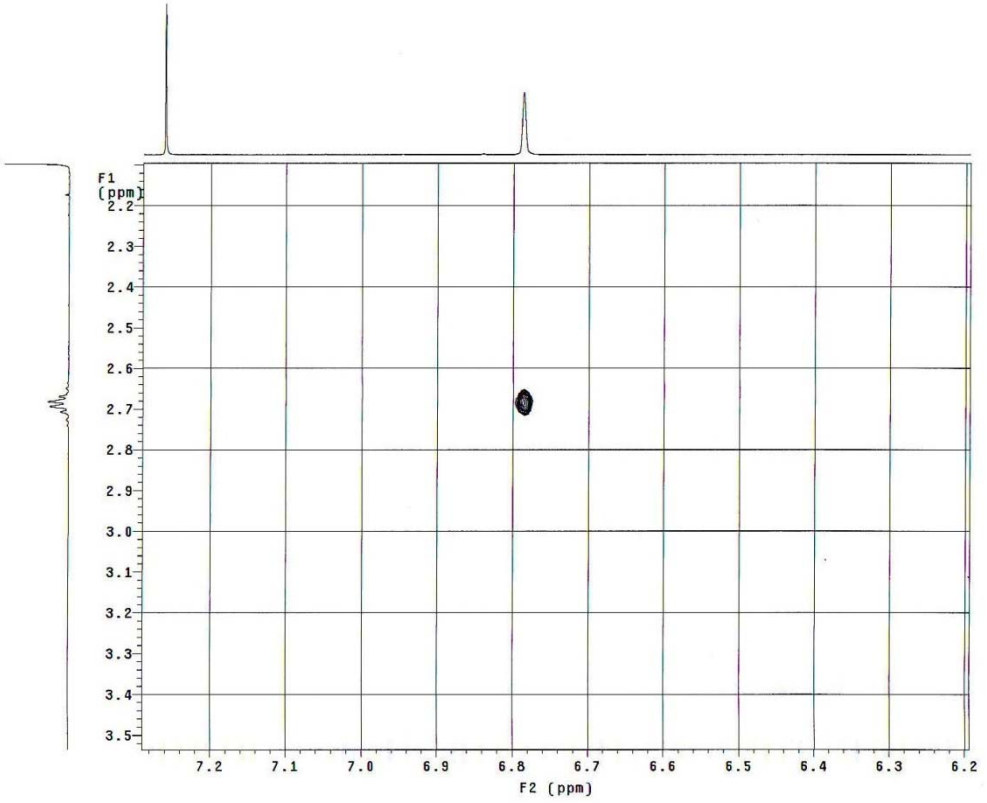
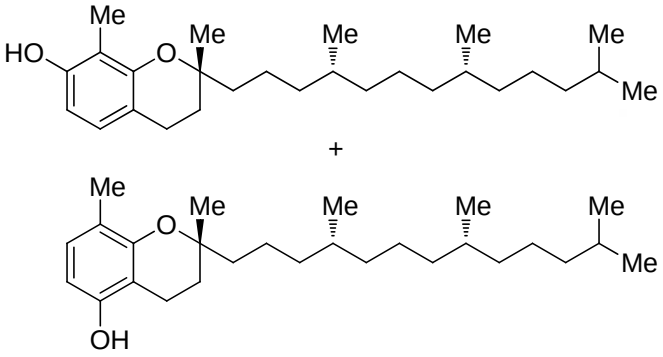
8
7
6
5
4
3
2
1
ppm

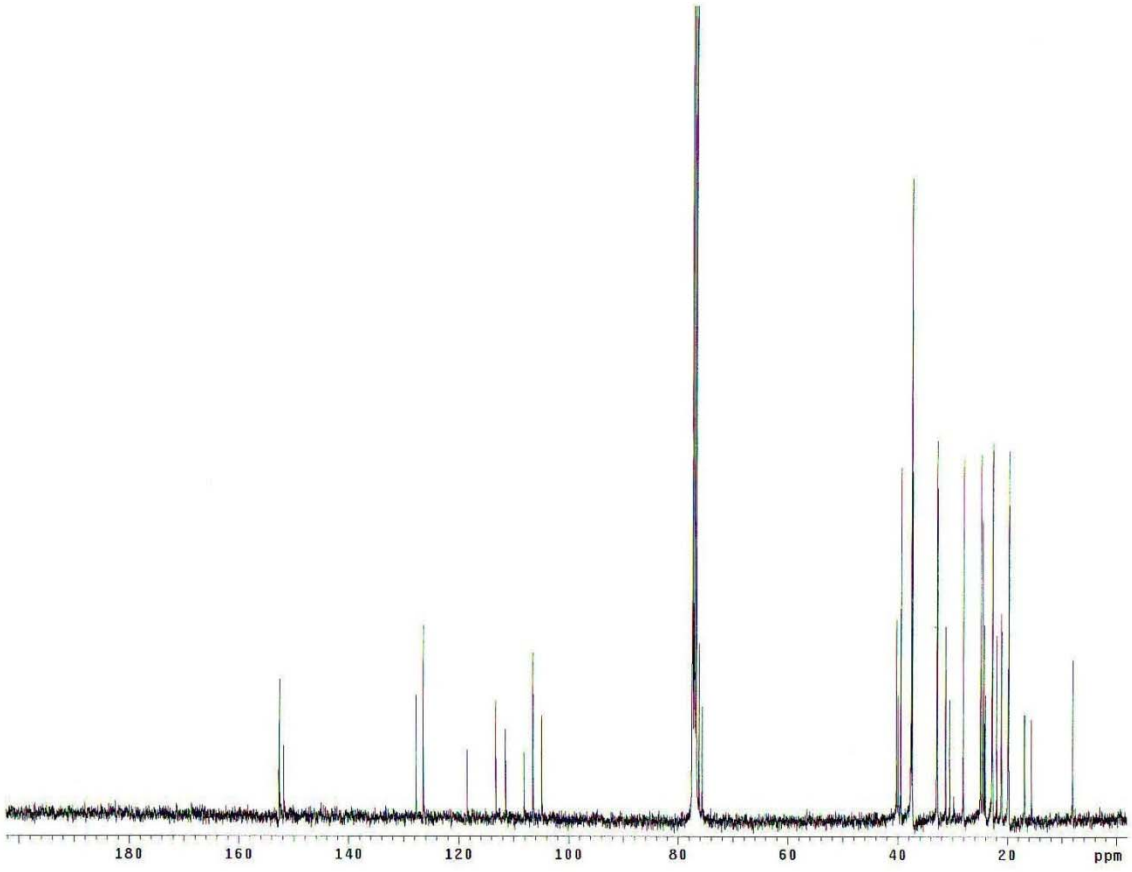

180
160
140
120
100
80
60
40
20
ppm


F1 (ppm)
F2 (ppm)


F1 (ppm)
F2 (ppm)


Me
HO
O
Me
Me
Me
Me
Me
+
Me
O
Me
Me
Me
Me
Me
OH

10
9
8
7
6
5
4
3
2
1
ppm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80
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20
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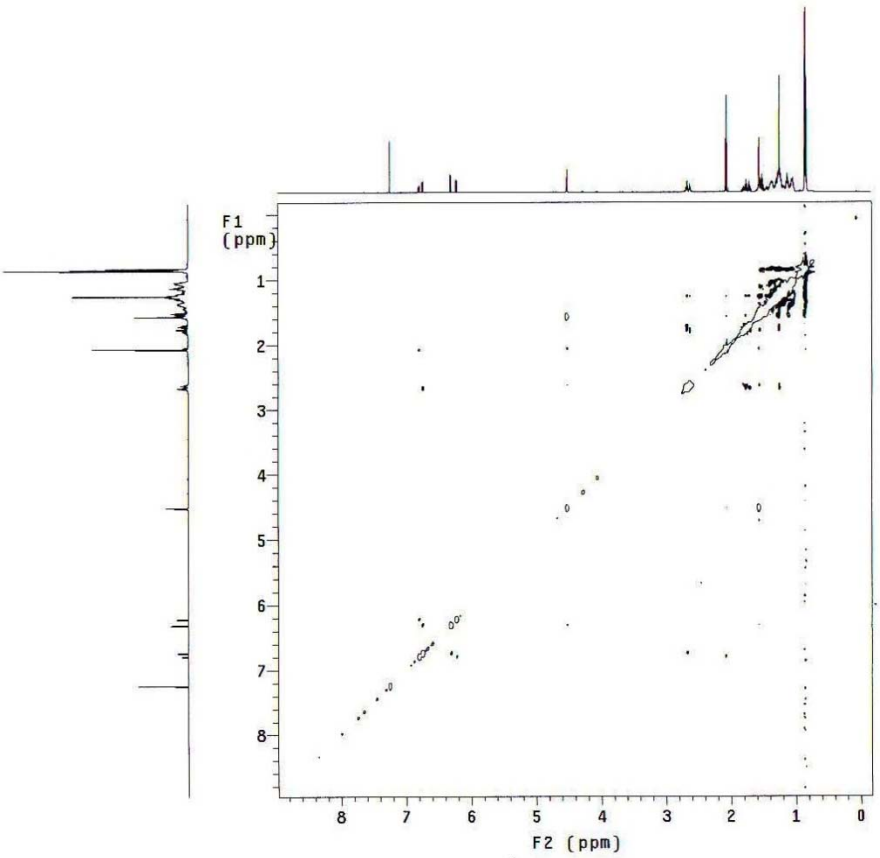
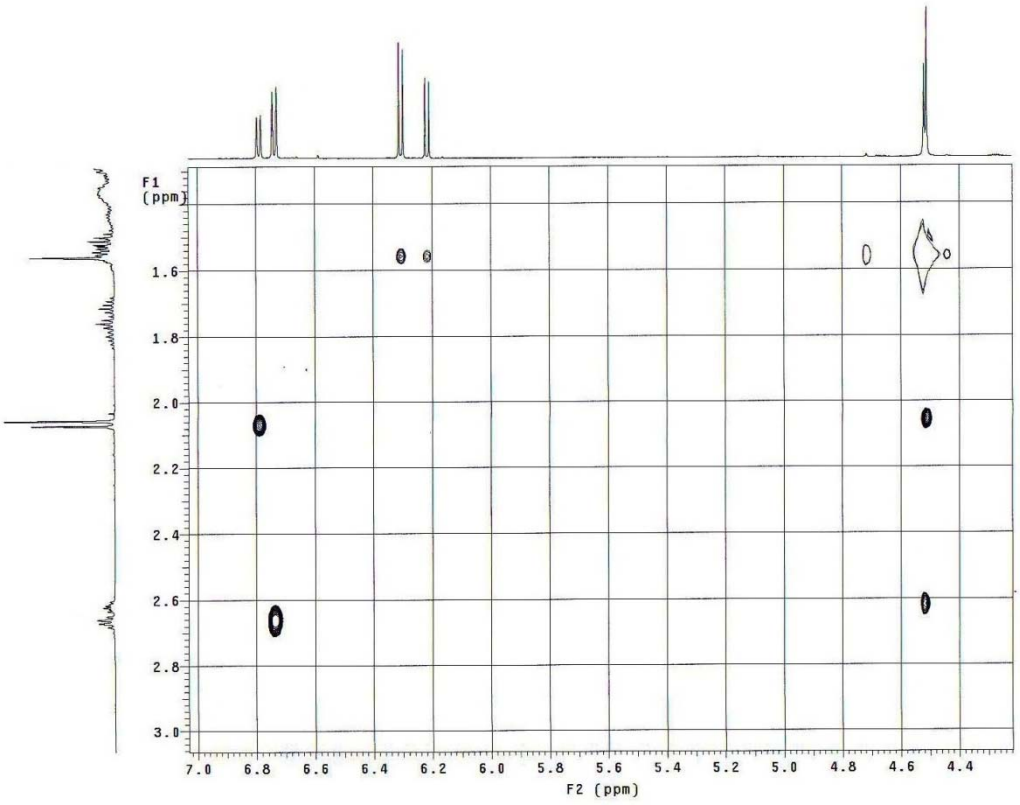

F1
(ppm)
1
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F2 (ppm)


F1
(ppm)
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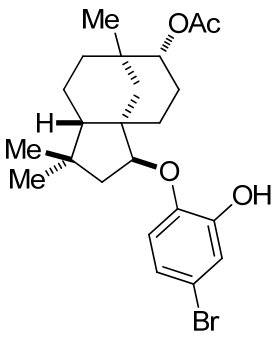
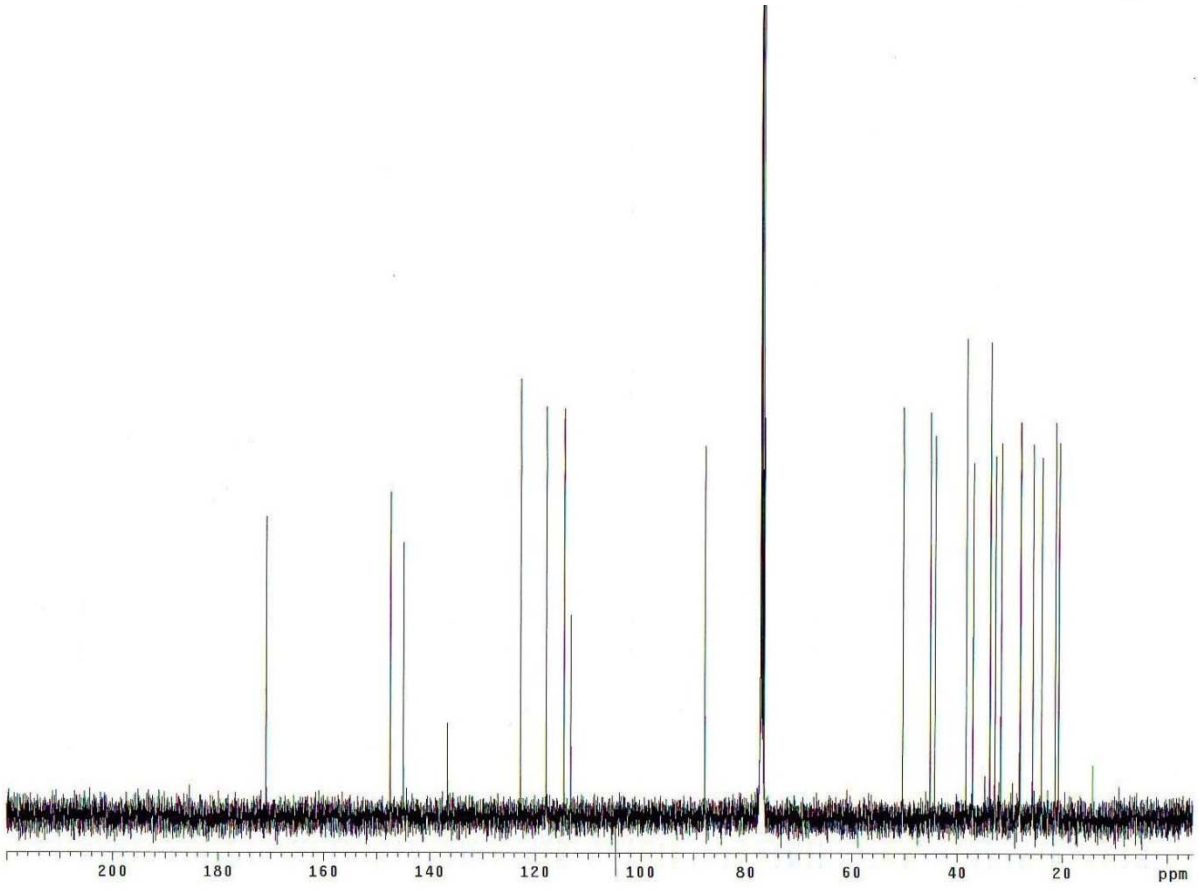
1.8
2.0
2.2
2.4
2.6
2.8
3.0
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
F2 (ppm)


Me
OAc
H
Me
Me
O
OH
Br

10
9
8
7
6
5
4
3
2
1
ppm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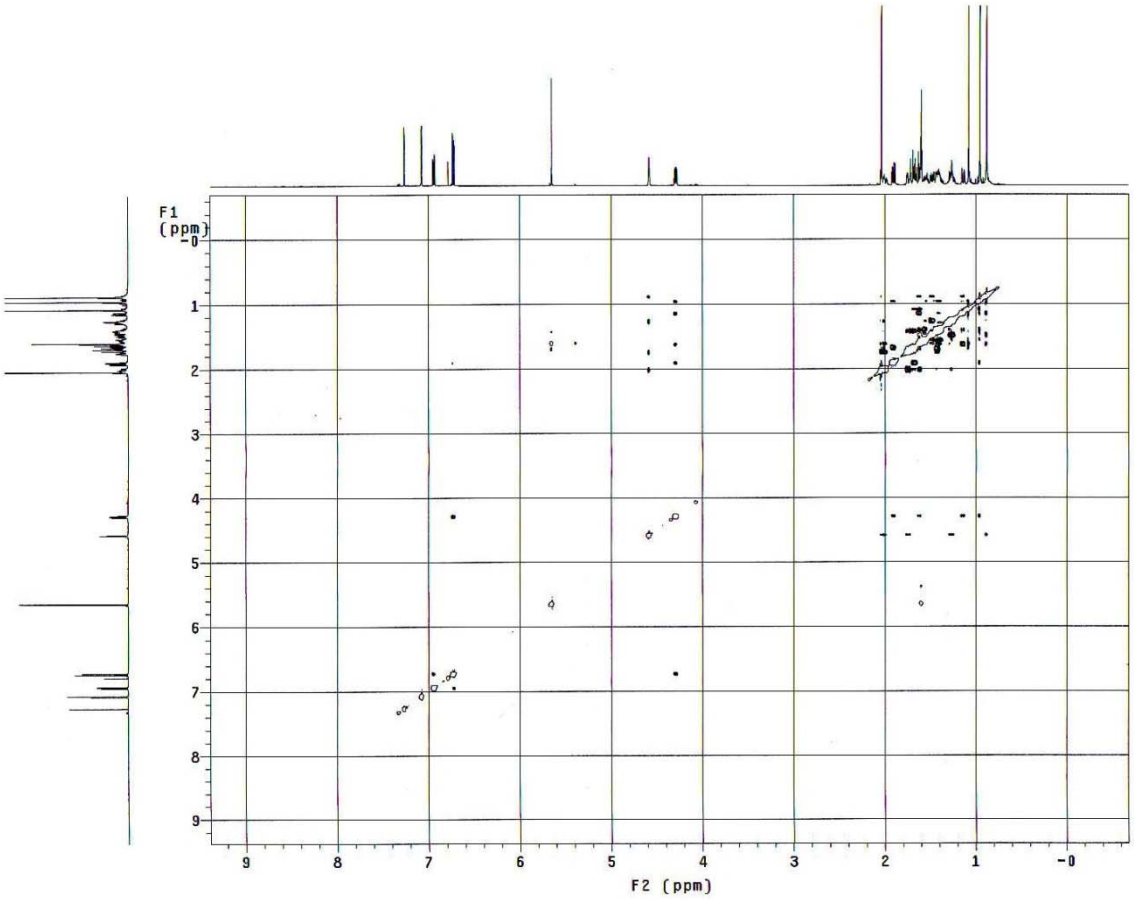
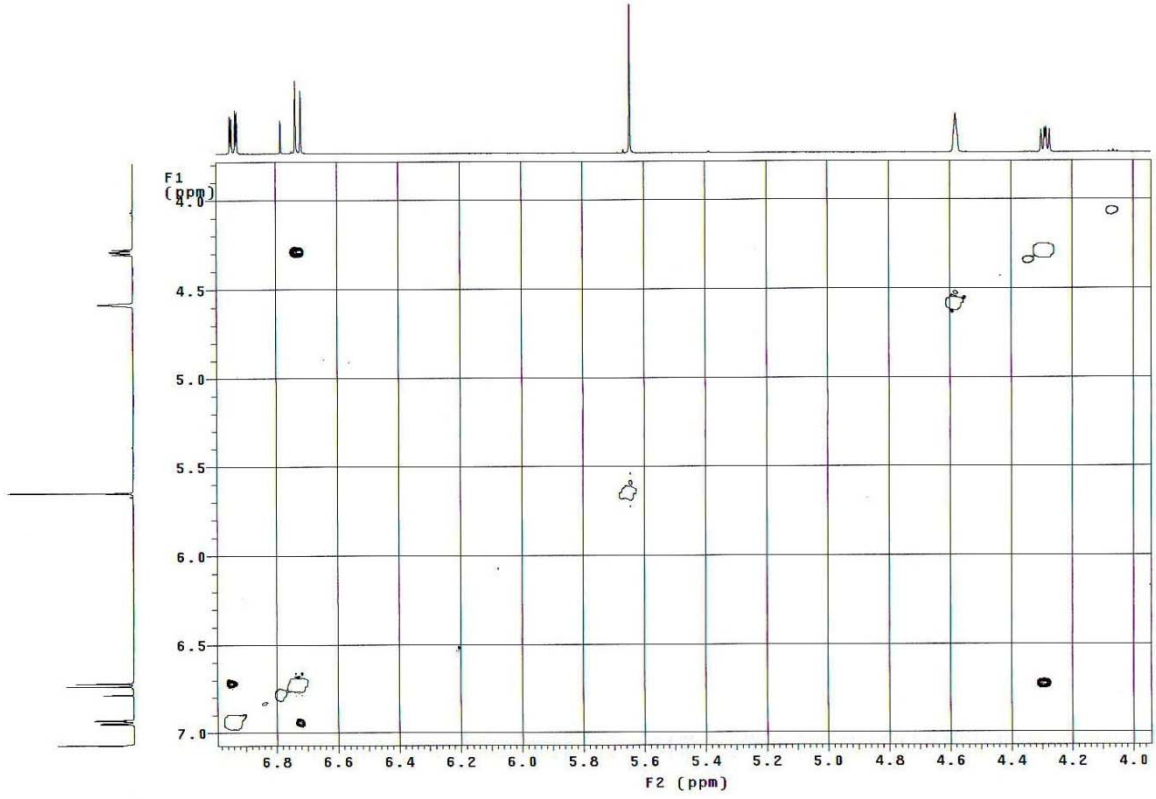
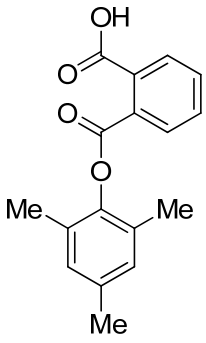
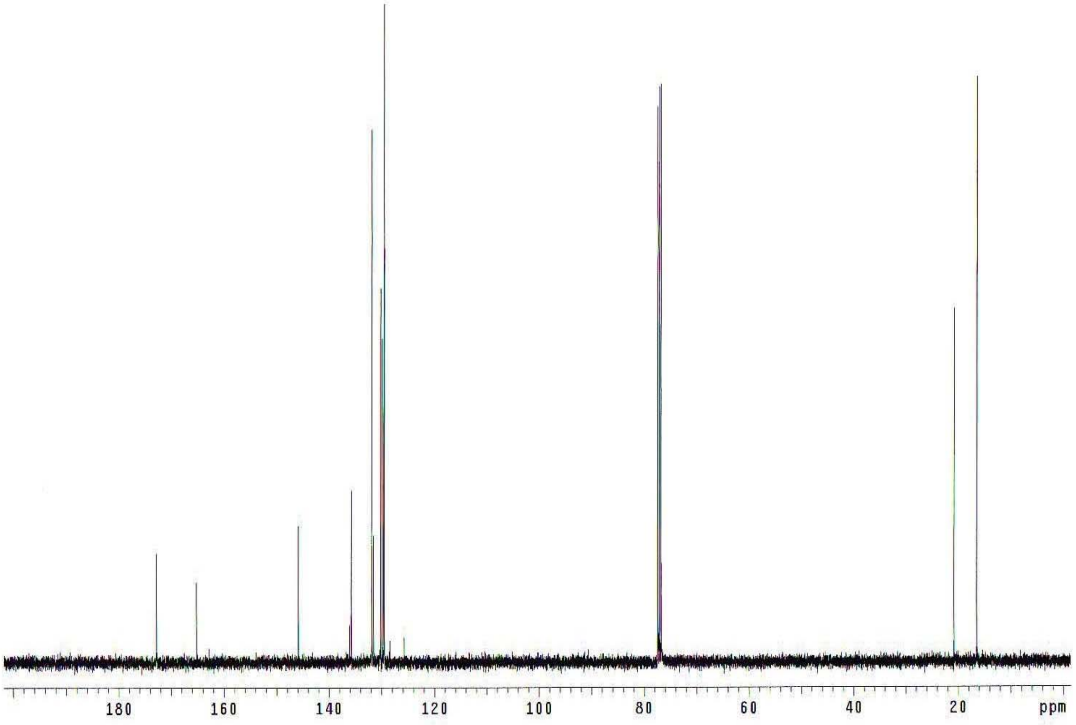
80
60
40
20
ppm


F1 (ppm)
F2 (ppm)


F1 (ppm)
F2 (ppm)


OH
O
O
O
Me
Me
Me

10
9
8
7
6
5
4
3
2
1
ppm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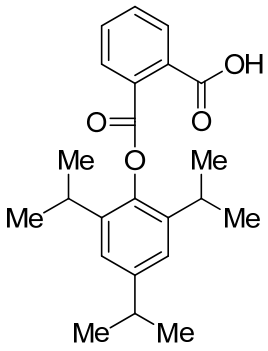
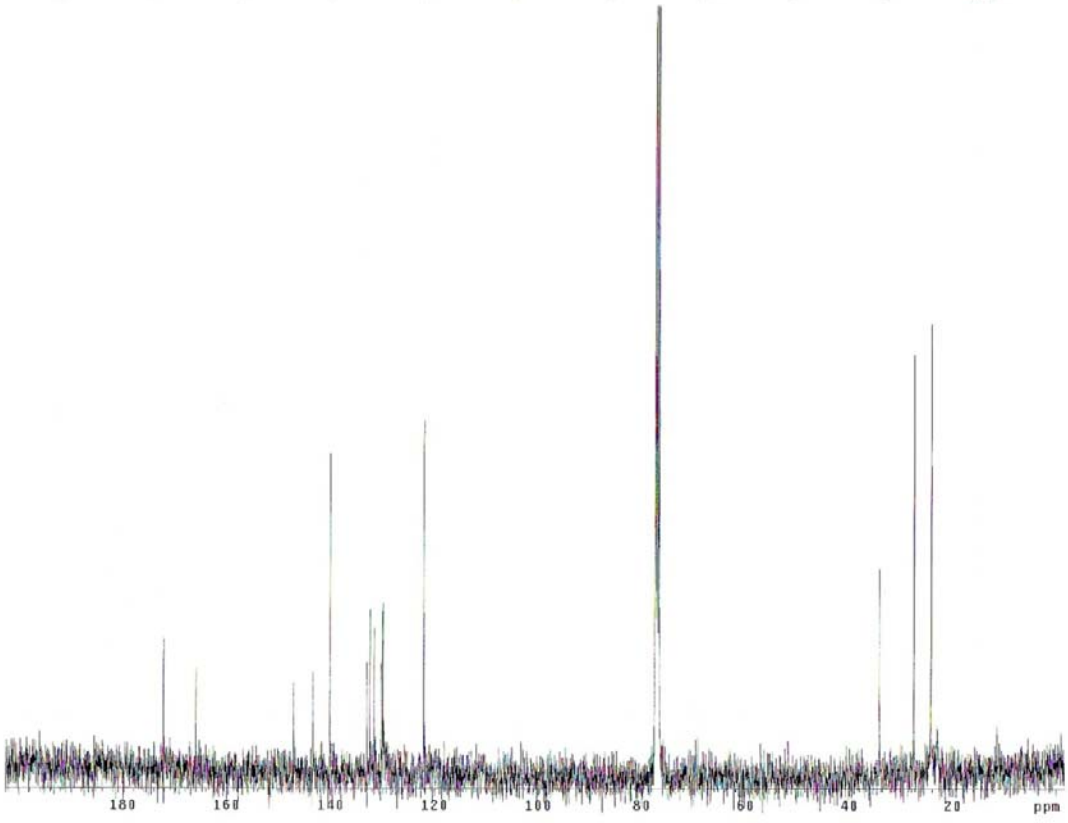
100
80
60
40
20
ppm


OH
O
O
Me
O
Me
Me
Me
Me
Me

10
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm